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# NON-TRADITIONAL RISK FACTORS FOR GESTATIONAL DIABETES MELLITUS

## IMPACT ON PREVALENCE AND OFFSPRING BIRTHWEIGHT

**Senja Masalin**

DOCTORAL DISSERTATION

To be presented for public discussion with the permission of the Faculty of Medicine of the University of Helsinki in the Seth Wichmann Auditorium, Department of Obstetrics and Gynecology, Helsinki University Hospital, on the 26th of March, 2021 at 12 o'clock.

Helsinki, 2021

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ISBN 978-951-51-6966-2 (pbk.)
ISBN 978-951-51-6967-9 (PDF)
http://ethesis.helsinki.fi

Unigrafia, Helsinki 2021

*To my family*
*and in memory of my father*

"Never stop learning, because life never stops teaching."- unknown

# ABSTRACT

Gestational diabetes mellitus (GDM) is a common metabolic pregnancy disorder, affecting 1 in 7 pregnancies on a global level. In Finland, the prevalence of GDM was estimated to around 21% in 2018 and the prevalence of GDM has been rapidly increasing. GDM is a major public health concern, with adverse short- and long-term health implications for the woman and her offspring. Traditional risk factors for GDM include advanced maternal age, overweight and obesity, a family history of diabetes and an ethnicity with a high prevalence of diabetes. There are, however, other risk factors, referred to as non-traditional, that have been shown to increase the risk for type 2 diabetes but have been studied less or with conflicting results with respect to GDM.

The aim of this thesis was to evaluate the impact of several non-traditional maternal risk factors (height, body size at birth, smoking status and socioeconomic status) on the risk for GDM.

In 2016, the Vantaa Birth Cohort study 2009-2015 was initiated, a follow-up register-based cohort study with the aim to evaluate the long-term health consequences of abnormal glucose regulation during pregnancy on the woman´s and her offspring´s health. Data were collected from national Finnish registers: the Finnish Medical Birth Register, the Finnish Social Insurance Institution, the Finnish Tax Administration, and Statistics Finland.

In Study I, encompassing 4,111 Finnish primiparous women and their singleton offspring, maternal height was inversely associated with the development of GDM, after adjustments for age and educational attainment ($p = 0.018$ for linearity). Independently, both maternal height and GDM were positively associated with the birthweight of the offspring (calculated as Z-score according to sex and gestational age; $p < 0.001$ for both). However, the interaction between maternal height and GDM was significant and an increase in offspring birthweight was noted only in women within extreme height categories, group I ≤ 158cm ($p = 0.011$), group IV 168–172cm ($p = 0.010$) and group V ≥ 173cm ($p < 0.001$).

In Study II, encompassing 1,548 Finnish primiparous women, there was a positive correlation between maternal body size at birth (assessed as body surface area [BSA]) and adult anthropometry. The association between maternal BSA at birth and GDM was inverse ($p = 0.015$ for linearity), after

adjustments for age, educational attainment, pre-pregnancy body mass index (BMI) and smoking.

In Study III, encompassing 4,111 Finnish primiparous women and their singleton offspring, a positive relationship between smoking during pregnancy and GDM was detected. The prevalence of GDM was highest in the group of smokers who continued smoking after the first trimester, compared with those who quit, and non-smokers ($p = 0.004$ for differences between groups). In women without GDM, birthweight was lowest in newborns of smokers who continued smoking after the first trimester ($p = 0.004$ for differences between groups, adjusted for age and pre-pregnancy BMI). In women with GDM, offspring birthweight was not related to maternal smoking.

In Study IV, encompassing 5,962 Finnish primiparous women, there was an inverse association between increasing maternal income level and the development of GDM, after adjustments for age, cohabiting status, pre-pregnancy BMI and smoking ($p < 0.001$ for linearity). Educational attainment also showed an inverse relationship with the development of GDM.

In conclusion, maternal current height, BSA at birth, and socioecomonic status (assessed as both income and education) were all inversely associated with the risk for development of GDM during pregnancy. Further, maternal smoking during pregnancy increased the risk for GDM. The birthweight was lowest in newborns of smoking women without GDM who continued smoking after the first trimester. However, among newborns of women with GDM, birthweight was not related to maternal smoking. Recognizing specific maternal risk factors is important in lifestyle counseling and targeted prevention of GDM. Hence, findings on the non-traditional risk factors evaluated in this thesis indicate they are of importance both from a clinical and public health perspective. However, future studies are needed to confirm the associations, taking possible additional confounding factors into account, as well as to verify the mechanisms behind these associations.

# TIIVISTELMÄ

Raskausdiabetes (GDM) on yleinen raskaudenaikainen metabolinen häiriö, joka diagnosoidaan joka seitsemännessä raskaudessa maailmanlaajuisesti. Suomessa vuonna 2018 GDM:n esiintyvyys oli arviolta noin 21 %. Viime vuosina GDM:n esiintyvyys on noussut merkittävästi. GDM on merkittävä kansanterveydellinen haaste, koska sillä on useita epäsuotuisia vaikutuksia äitiin ja sikiöön sekä lyhyellä että pitkällä aikavälillä. Perinteisiä GDM:n riskitekijöitä ovat äidin korkea ikä, ylipaino ja lihavuus, lähisukulaisella esiintyvä diabetes ja etninen tausta johon liittyy kohonnut diabetesriski. Tämän lisäksi on ei-perinteisiä riskitekijöitä, joiden on todettu lisäävän tyypin 2 diabeteksen riskiä, mutta joita GDM:n suhteen on tutkittu joko vähemmän tai joiden vaikutukset GDM:n riskin suhteen ovat olleet ristiriitaisia.

Tämän väitöskirjatutkimuksen tarkoitus oli selvittää synnyttäjän ominaisuuksien ja eräiden ei-perinteisten riskitekijöiden (pituus, syntymäkoko, tupakointi raskauden aikana sekä sosioekonominen asema) vaikutuksia GDM:n esiintyvyyteen.

Vuonna 2016 käynnistettiin rekisteripohjainen Vantaan syntymäkohortti 2009-2015 seurantatutkimus. Tutkimuksen tavoite on selvittää raskaudenaikaisen poikkeavan glukoosiaineenvaihdunnan seurauksia naisen ja lapsen myöhempään terveydentilaan. Tietoja naisista ja lapsista on kerätty Valtakunnallisesta syntymärekisteristä, Kansaneläkelaitokselta, Tilastokeskuksesta ja Verohallinnolta.

Osatyössä I, jonka aineiston muodostivat 4 111 suomalaista ensisynnyttäjää ja heidän lapsensa, synnyttäjän pituus oli käänteisesti yhteydessä GDM:n esiintyvyyteen (lineaarisuuden suhteen $p = 0.018$, korjattu iällä ja koulutustasolla). Yksinään sekä pituus että GDM lisäsivät vastasyntyneen syntymäpainoa, joka laskettiin Z-arvona huomioiden raskauden kesto syntyessä ja lapsen sukupuoli (molemmat $p < 0.001$). Äidin pituuden ja GDM:n välillä oli kuitenkin merkittävä yhdysvaikutus siten, että lapsen syntymäpaino nousi merkitsevästi ainoastaan pituuden ääriryhmissä GDM-äideillä (ryhmä I ≤ 158cm [$p = 0.011$], ryhmä IV 168–172cm [$p = 0.010$] ja ryhmä V ≥ 173cm [$p < 0.001$]).

Osatyössä II, jonka aineiston muodostivat 1 546 suomalaista ensisynnyttäjää, äidin syntymäkoko (arvioitu kehon pinta-alana, body surface area [BSA]) oli myönteisesti yhteydessä äidin aikuisantropometriaan. BSA:n ja GDM:n

yhteys oli käänteinen (lineaarisuuden suhteen p = 0.015, korjattu äidin iällä, koulutustasolla, raskautta edeltävällä painoindeksillä ja tupakoinnilla).

Osatyössä III, jonka aineiston muodostivat 4 111 suomalaista ensisynnyttäjää ja heidän vastasyntyneensä, äidin raskauden aikainen tupakointi lisäsi GDM:n esiintyvyyttä. GDM:n esiintyvyys oli korkein niiden naisten ryhmässä, jotka jatkoivat tupakointia ensimmäisen raskauskolmanneksen jälkeen, verrattuna heihin, jotka lopettivat tai eivät olleet tupakoineet lainkaan (ryhmien välinen ero p= 0.004). Vastasyntyneen syntymäpaino oli matalin niiden naisten ryhmässä, jotka jatkoivat tupakointia ensimmäisen raskauskolmanneksen jälkeen (ryhmien välinen ero p = 0.004, korjattu äidin iällä ja raskautta edeltävällä painoindeksillä). Mikäli raskaana olevalla naisella todettiin GDM, lapsen syntymäpainossa ei todettu ryhmien välistä eroa suhteessa tupakointiin.

Osatyössä IV, jonka aineiston muodostivat 5 962 suomalaista ensisynnyttäjää, äidin tulotaso oli käänteisesti yhteydessä GDM:n esiintyvyyteen (lineaarisuuden suhteen p < 0.001, korjattu äidin iällä, raskautta edeltävällä painoindeksillä, tupakoinnilla ja parisuhteella). Äidin korkeammalla koulutustasolla todettiin olevan suojaava vaikutus GDM:n esiintyvyyteen.

Yhteenvetona voidaan tämän väitöskirjan pohjalta todeta, että raskaana olevan naisen pituus, oma syntymäkoko ja sosioekonominen asema (arvioitu tulotason ja koulutustason perusteella) ovat käänteisesti yhteydessä GDM:n kehittymiseen. Äidin tupakointi raskauden aikana lisää GDM:n riskiä. Riski vastasyntyneen pieneen syntymäpainoon on suurempi tupakointia ensimmäisen raskauden jälkeen jatkavilla naisilla, joille ei kehity GDM. GDM-äideillä ei vastaavaa ilmiötä todettu. GDM:n kohdennetussa ennaltaehkäisevässä työssä ja elämäntapaohjauksessa riskitekijöiden tunnistaminen on tärkeätä. Tutkimustuloksemme nostavat esiin ei-perinteisten riskitekijöiden tärkeyden niin kliinisessä työssä kuin kansanterveydenkin kannalta. Aiheeseen liittyviä lisätutkimuksia tarvitaan vahvistamaan havaitsemiamme yhteyksiä sekä selvittämään taustalla vaikuttavia biologisia mekanismeja.

# SAMMANFATTNING

Graviditetsdiabetes (GDM) är en allmänt förekommande störning i glukosämnesomsättningen, som kan drabba gravida kvinnor. Globalt uppskattas var sjunde gravida kvinna drabbas av störningen och i Finland rapporterades förekomsten av GDM ligga omkring 21% år 2018. GDM påverkar den gravida kvinnan samt fostret på ett ogynnsamt sätt både på kort och lång sikt och då förekomsten av störningen under det senaste decenniet ökat dramatiskt är GDM idag ett stort problem för folkhälsan. Traditionella riskfaktorer för GDM är moderns höga ålder, övervikt och fetma, förekomst av diabetes inom familj eller när-släkt samt ett etniskt ursprung med hög förekomst av diabetes. Utöver dessa finns ett flertal icke-traditionella riskfaktorer, som har konstaterats öka risken för typ 2 diabetes, men som har undersökts sparsamt eller med motstridiga resultat i förhållande till GDM.

Avsikten med denna avhandling är således att undersöka hur ett flertal icke-traditionella riskfaktorer och den gravida kvinnans egenskaper (längd, födelsestorlek, rökning under graviditeten samt socioekonomiska status) påverkar förekomsten av GDM.

År 2016 inleddes Vanda födelsekohort 2009-2015 forskningsprojektet, med syfte att undersöka effekterna av en avvikande glukosmetabolism under graviditeten på lång sikt för modern och barnet. Uppgifter om mödrarna och barnen har samlats från nationella register i Finland: det medicinska födelseregistret, Folkpensionsanstalten (FPA), Statistikcentralen, och Skatteförvaltningen.

I delarbetet I, som omfattade 4 111 finländska förstföderskor och deras barn, konstaterades moderns längd ha ett inverst förhållande till förekomsten av GDM ($p = 0.018$ för linearitet, justerat för moderns ålder samt utbildning). Korta kvinnor var således i högsta risk att utveckla GDM. Både moderns tilltagande längd och GDM hade en ökande effekt på den nyföddes födelsevikt (beräknat som Z-värde genom att beakta kön och graviditetens längd) ($p < 0.001$ för båda). Interaktionen mellan moderns längd och GDM var dock signifikant, således att den nyföddas födelsevikt ökade märkbart endast i de grupper av kvinnor som var väsentligt kortare eller längre än kvinnorna av medel-längd (grupp I ≤ 158cm [$p = 0.011$], grupp IV 168–172cm [$p = 0.010$] och grupp V ≥ 173cm [$p < 0.001$]).

I delarbetet II, som omfattade 1 546 finländska förstföderskor, konstaterades moderns födelsestorlek (uppskattat som kroppsyta, body surface area [BSA])

korrelera med vuxen antropometri samt ha ett inverst förhållande till förekomsten av GDM ($p = 0.015$ för linearitet, justerat för moderns ålder, utbildningsgrad, kroppsmassa-index (body mass index [BMI]) innan graviditeten samt rökning under graviditeten). Kvinnor som var små vid födseln hade största risk att utveckla GDM.

I delarbetet III, som omfattade 4 111 finländska förstföderskor och deras barn, konstaterades moderns rökning under graviditeten öka risken för GDM. Förekomsten av GDM var högst i den grupp av kvinnor, som fortsatte röka efter den första graviditetstrimestern då man jämförde med de kvinnor som slutade röka eller aldrig hade rökt under graviditeten ($p = 0.004$ för skillnaden mellan grupperna). Den nyföddes födelsevikt var lägst i den grupp av kvinnor, som fortsatte röka efter den första trimestern ($p = 0.004$ för skillnaden mellan grupper, justerat för moderns ålder samt BMI innan graviditeten). Ifall GDM konstaterats under pågående graviditet, skilde sig inte den nyföddas födelsevikt mellan grupperna i hänseende till rökning.

I delarbetet IV, som omfattade 5 962 finländska förstföderskor, konstaterades moderns inkomster och utbildningsgrad även ha ett inverst förhållande till förekomsten av GDM ($p < 0.001$ för linearitet, justerat för moderns ålder, BMI innan graviditet, rökning samt samboende-status). Kvinnorna med lägsta inkomst hade således den största risken för att utveckla GDM. Moderns högre utbildningsgrad hade en skyddande effekt för GDM.

Sammanfattningsvis kan konstateras att moderns längd, födelsestorlek och socioekonomiska ställning (beräknat utgående från inkomster och utbildningsgrad) förhåller sig omvänt till risken för att utveckla GDM. Ytterligare kan framhållas, att moderns rökning under graviditeten ökar risken för GDM. Hos kvinnor, som fortsätter röka efter den första graviditetstrimestern finns en förhöjd risk för en låg födelsevikt hos den nyfödda. Den nyföddes födelsevikt skiljer sig trots allt inte i förhållande till moderns rökningsbeteende hos kvinnor med GDM. I ett förebyggande syfte samt för en målinriktad livsstilsrådgivning är det viktigt att känna till riskfaktorer för GDM. Identifieringen av de icke-traditionella riskfaktorerna i denna avhandling verkar vara av betydelse i såväl kliniskt arbete som ur ett mera omfattande folkhälsoperspektiv. Dock krävs det framtida studier för att bekräfta dessa samband genom att kontrollera för kända störfaktorer samt för att utreda de biologiska mekanismerna bakom sambandena.

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# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following four publications:

I Masalin S, Laine MK, Kautiainen H, Gissler M, Raina M, Pennanen P, Eriksson JG. Impact of maternal height and gestational diabetes mellitus on offspring birthweight. Diabetes Res Clin Pract. 2019;148:110-118.

II Masalin S, Rönö K, Kautiainen H, Gissler M, Eriksson JG, Laine MK. Body surface area at birth and later risk for gestational diabetes mellitus among primiparous women. Acta Diabetol. 2019;56(4):397-404.

III Masalin S, Kautiainen H, Gissler M, Pennanen P, Eriksson JG, Laine MK. Impact of smoking on gestational diabetes mellitus and offspring birthweight in primiparous women. Acta Obstet Gynecol Scand. 2020; 99(12):1632-1639.

IV Rönö K, Masalin S, Kautiainen H, Gissler M, Raina M, Eriksson JG, Laine MK. Impact of maternal income on the risk of gestational diabetes mellitus in primiparous women. Diabet Med. 2019;36(2):214-220.

The original publications are reprinted with permission from the publishers. In the text, the publications are referred to by their Roman numerals. This thesis also includes some previously unpublished data.

Study IV, with shared authorship, is also included in the Doctoral Thesis of Kristiina Rönö, published in 2019.

# ABBREVIATIONS

| | |
|---|---|
| ADA | American Diabetes Association |
| BMI | body mass index |
| BSA | body surface area |
| CI | confidence interval |
| cm | centimeters |
| DOHaD | Developmental Origins of Adult Health and Disease |
| g | gram |
| gw | gestational weeks |
| GDM | gestational diabetes mellitus |
| h | hour |
| HAPO | Hyperglycemia and Adverse Pregnancy Outcome Study |
| HbA1c | glycated hemoglobin |
| IADPSG | International Association of the Diabetes and Pregnancy Study Groups |
| ICD-10 | International Statistical Classification of Disease and Related Health Problems 10th Revision |
| IR | insulin resistance |
| kg | kilograms |
| LGA | large for gestational age |
| mmol/L | millimoles per liter |
| NDDG | National Diabetes Data Group |
| NICE | National Institute for Health and Care Excellence |
| OGTT | oral glucose tolerance test |
| OR | odds ratio |
| PI | ponderal index |
| SD | standard deviation |
| SGA | small for gestational age |
| SES | socioeconomic status |
| T1D | type 1 diabetes |
| T2D | type 2 diabetes |
| THL | National Institute for Health and Welfare |
| USA | United States of America |
| WHO | World Health Organization |
| € | euro |

# 1 INTRODUCTION

Research on diabetes during pregnancy has been intense ever since the first description over 200 years ago of a pregnant woman in England having symptoms of diabetes and significant glucosuria, who gave birth to a stillborn macrosomic infant. Extensive progress in prognosis for both the mother and the offspring has been achieved thanks to updated diagnostic strategies and improved medical treatment and pregnancy follow-up. However, diabetes during pregnancy is still a major concern with both short- and long-term adverse effects on the mother and her offspring. Today, hyperglycemia detected for the first time during pregnancy is subclassified into overt/pre-existing diabetes (type 1 diabetes [T1D]/ type 2 diabetes [T2D]) or gestational diabetes mellitus (GDM), depending on the timing of diagnosis (1) or diagnostic thresholds applied (2). Nevertheless, despite several international workshops among the scientific community, a universal consensus for the best screening and diagnostic strategies of GDM is still missing.

The prevalence of GDM has globally increased during the recent decades (3-7), at least partly due to an increase in childbearing age (3) and increased rates of obesity (3) and impaired glucose tolerance and T2D in background populations (8-10). The estimated global prevalence of hyperglycemia during pregnancy was 16% in 2019, of which 84% were classified as GDM, according to the International Diabetes Federation (10). In Finland, the estimated GDM prevalence has more than doubled within a decade and was 21% in 2018, according to the Finnish Medical Birth Register (7).

From a short-term perspective, GDM increases the risk for fetal overgrowth known as macrosomia (11), induction of labor, maternal pelvic floor injuries, shoulder dystocia, operative vaginal deliveries and cesarean sections (11, 12). Moreover, admissions to neonatal intensive care units due to fetal hypoglycemia and fetal distress are more common among the newborns of women with GDM (11, 13). From a long-term perspective, GDM is known to increase the risks for abnormal glucose tolerance and T2D, cardiovascular diseases and other metabolic disorders in both the woman and her offspring (13-17). Thus, the importance of an efficient GDM prevention and treatment has been further emphasized along with the understanding that the intrauterine milieu may have long-spanning effects on adult health (18, 19).

Well-acknowledged traditional risk factors for GDM include advanced maternal age, increased body mass index (BMI), a family history of diabetes mellitus, fetal macrosomia in a previous pregnancy, and an ethnicity with a

high prevalence of diabetes (20-22). However, there are many risk factors that have been reported to increase the risk for T2D, but have been studied less or with conflicting results with respect to development of GDM. These risk factors are referred to as non-traditional in this thesis and of these, the effect of maternal height, birth size (evaluated as body surface area, BSA), smoking during pregnancy and socioeconomic status (SES) will be evaluated.

Although rather scarcely studied, the majority of previous studies have reported maternal short stature to increase the risk for GDM (23). Similarly, maternal low birthweight is reported to increase the risk for GDM, but maternal size at birth using BSA as an indicator has not been evaluated before. Findings regarding the relationship between maternal smoking during pregnancy and GDM remain conflicting (24, 25). Similarly, in many studies the relationship between SES and GDM seems to be inverse (26-28), although neutral relationships have also been reported (29, 30). However, using different indicators for SES makes comparisons between studies difficult. Thus far, no previous studies have assessed the impact of objectively reported maternal annual mean income on the risk for GDM in a Scandinavian population.

GDM is a growing public health concern, not just with respect to the suffering on an individual level, but also with respect to the cost for the whole society (31, 32). The aim of this thesis is to evaluate the associations of several non-traditional risk factors (maternal height, BSA at birth, smoking during pregnancy, and SES assessed as income and educational attainment) with GDM. When recognized and acknowledged, these risk factors could serve as additional tools in the identification of women at high risk for GDM and assist in an effective targeting of interventions.

# 2 REVIEW OF THE LITERATURE

## 2.1 HISTORICAL ASPECTS AND DEFINITION OF GESTATIONAL DIABETES MELLITUS

The first clinical case of a woman with classical symptoms of diabetes in three successive pregnancies is described in the literature in the year 1824 by Heinrich Bennewitz in Germany (33). In 1882, James Duncan published the first series of diabetic pregnancies in London and reported a maternal mortality of 60% and a newborn mortality of 47% (34). Further, he concluded that "pregnancy may occur during diabetes", and "varies in occurrence" (34).

During the latter half of the 19th century pregnant women were described to be less tolerant to sugar and interests in pathological glucosuria arose (35). In 1909, interpretations of the clinical significance of glucosuria in pregnant women were published (35). Blood glucose testing and glucose challenge testing for diagnostic purposes were introduced in the 1920s and early 1930s (35).

A remarkable turning point in the history of diabetes was the discovery of insulin in 1921 (36). A dramatic improvement in maternal mortality among pregnant women with diabetes was noticed, but only modest improvement was seen in neonatal outcomes and survival (34, 35) – this would take several decades to achieve due to later improvements in assessing and optimizing glycemic control, evaluating fetal–placental function, and determining fetal growth, well-being and lung maturity, as well as by optimizing time of delivery (34).

The significance of milder or asymptomatic hyperglycemia causing adverse pregnancy outcomes was recognized in the 1940´s. In 1945, Herbert Miller reported adverse obstetric and perinatal outcomes in pre-diabetic mothers, those diagnosed with diabetes mellitus only after pregnancy, and their newborns (37). In the 1950s the term gestational diabetes mellitus (GDM) was introduced (35). At the same time, a Danish epidemiologist, Jørgen Pedersen, defended his doctoral thesis about the effects of maternal hyperglycemia resulting in fetal hyperinsulinemia causing exaggerated fetal growth or macrosomia (38).

In 1964, the World Health Organization (WHO) stated that gestational diabetes refers to "hyperglycemia of diabetic levels (similar to non-pregnant adults) occurring during pregnancy" (39). However, the first diagnostic criteria considered as a gold standard of GDM diagnosis were published by

O'Sullivan and Mahan in 1964 (40). Ever since, the diagnostic criteria have been a topic of debate.

For decades the definition of GDM remained the same, stated in 1979 at the First International Workshop of GDM as "glucose intolerance recognized during pregnancy" (41), and re-formulated to "carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy" at the fourth International Workshop in 1998 (42) – at that time, diabetes that could have antedated pregnancy was not excluded.

Along with the epidemic of T2D, the prevalence of undiagnosed T2D among pregnant women has also increased (8, 43, 44). Considering the adverse pregnancy outcomes associated with overt diabetes (45), new definitions of hyperglycemia during pregnancy had been proposed. In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended high-risk women found to have diabetes at their initial prenatal visit, to receive a diagnosis of overt, not gestational diabetes (44, 46). Similarly, in 2013, the WHO recommended to subclassify hyperglycemia during pregnancy as either "diabetes mellitus in pregnancy" or "gestational diabetes mellitus" based on different diagnostic threshold values in oral glucose tolerance tests (OGTT), independent of timing of diagnosis (1). However, the most recent definition of GDM is suggested by the American Diabetes Association (ADA) as "diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation" (2, 47).

# 2.2 GESTATIONAL DIABETES MELLITUS

## 2.2.1 ETIOLOGY AND PATHOPHYSIOLOGY

### *2.2.1.1 Glucose metabolism in normal pregnancy*

The maternal body goes through complex metabolic changes in glucose, fatty- and amino-acid metabolism during pregnancy – primarily to ensure sufficient nutrients for the growing fetus, as well as to prepare the woman for the increased energy demands of pregnancy, delivery and lactation (48). For the growing fetus, glucose is the primary source of energy since the fetus is almost totally dependent on maternal plasma glucose due to the lack of its own significant gluconeogenesis (49).

*Early pregnancy*

During the first trimester, glucose tolerance is considered as normal, or even slightly improved (50), due to an increased insulin response to oral glucose administration (51, 52). During early pregnancy, the first-phase insulin response is increased. This refers to the immediate secretion of insulin that occurs 0–5 minutes after a rise in blood glucose concentration, in contrast to the second-phase of insulin response that occurs 5–60 minutes after the initial increase in glucose concetrations (50). However, the sensitivity of skeletal muscle and other peripheral tissues to insulin and basal glucose production in the liver are considered similar to the pre-gravid state. Thus, the metabolic milieu of early pregnancy favors an anabolic state of maternal lipogenesis and adipose tissue accretion (50) for utilization in later pregnancy and the postpartum period (48). Fasting glucose concentrations decrease slightly across pregnancy until the third trimester, likely due to the dilutional effects of increased blood volume and the fetoplacental glucose utilization later in pregnancy (48, 50, 53, 54).

*Late pregnancy*

The latter half of pregnancy is characterized by insulin resistance (IR) that increases progressively toward the third trimester to a level seen in individuals with T2D (55). The increase in IR leads to a reduced uptake of glucose in maternal peripheral tissues, as well as to an increase in endogenous gluconeogenesis as the liver is more resistant toward the response to insulin. Insulin sensitivity can be reduced as much as 33–78% during late pregnancy (50, 56, 57). The compensatory increase in insulin response to glucose of up to 200% (56) is associated with pancreatic β-cell hypertrophy and hyperplasia (58), and the robust plasticity of the cells is crucial for a normal glucose

homeostasis (55). In healthy pregnancies, maternal glucose levels are maintained within rather narrow margins (56).

The etiology of IR is multifactorial and not completely understood. The increase in maternal adipose tissue in late pregnancy, as well as the increase in placental and other growth–promoting hormones (such as placental lactogen, placental growth hormone, progesterone, estrogen, cortisol) and proinflammatory cytokines (such as tumor necrosis factor alfa, TNF-a) are implicated behind the phenomenon (22, 54, 59). To ensure a continuous glucose supply to the fetus, maternal glucose metabolism changes during both the fed and fasting state (48). After a meal, maternal metabolic adaptions, referred to as "facilitated anabolism", promote heightened postprandial glucose concentrations, as well as lipid concentrations, compared to the pre-pregnancy state. During the fasting state, on the other hand, glucose concentrations decrease profoundly, and enhanced gluconeogenesis of the liver ensures a continuous glucose supply to the fetus, with a concomitant increase in free fatty acids compared to the non-pregnant state. These metabolic changes are referred to as "accelerated starvation" (48).

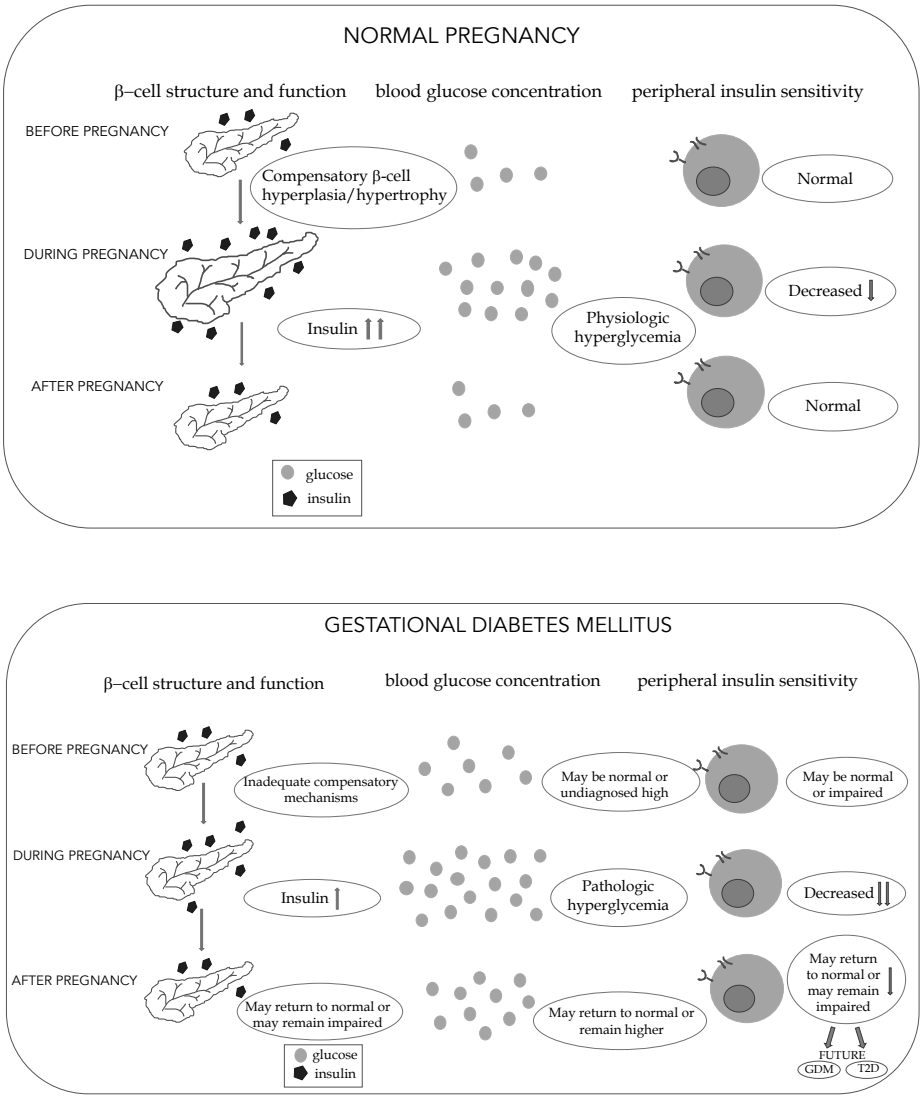
Typically, within the first days after delivery, glucose and insulin metabolism are re-established as fasting insulin levels (48), and insulin sensitivity returns to pre-pregnancy levels (60).

#### *2.2.2.2. Pathophysiology of gestational diabetes*

GDM is a heterogenous disorder and its pathophysiology is not yet fully understood. However, GDM is characterized by a variable degree of hyperglycemia mainly due to chronic IR and/or pancreatic β-cell dysfunction superimposed on the metabolic changes of pregnancy (60).

The majority of women, over 80%, who develop GDM tend to have β- cell dysfunction occurring on a background of chronic insulin resistance (22, 55), as schmatically illustrated in Figure 1. The driver behind hyperglycemia can be both a defect in insulin secretion or a defect in insulin sensitivity (61), and women who develop GDM seem to have a sub-clinical metabolic dysfunction already prior to gestation (62). The dysfunction includes impaired first phase insulin secretion, peripheral insulin resistance, and decreased hepatic suppression of glucose production by insulin (50), leading to clinical hyperglycemia in late gestation (62) as their insulin secretion is insufficient to meet the additional requirements of pregnancy (51, 55, 63). Alterations in the post-receptor insulin signaling pathway seem to play a role in the decreased insulin sensitivity (55, 63) and chronic IR is thought to, in the long term,

exhaust the β-cells and lead to an even greater discrepancy in insulin and glucose balance (64), contributing to the development of T2D.




*GDM*, gestational diabetes mellitus; *T2D*, type 2 diabetes

**Figure 1** Schematic illustration of glucose metabolism during normal pregnancy and in women with gestational diabetes mellitus. Redrawn with modifications from Plows et al., The Pathophysiology of Gestational Diabetes Mellitus. Int J Mol Sci. 2018;19. MDPI, Basel, Switzerland (CC BY license).

Even though the heterogeneity of GDM is acknowledged, many women with GDM tend to be overweight. In a recent Swedish study, 70% were reported to be overweight or obese (65). Mechanisms of cytokines and inflammatory markers linking obesity to insulin resistance are therefore also likely to play a role in the pathophysiology of GDM. Increased content of fat in peripheral tissue has been reported in women with prior GDM (55, 66). Recent evidence suggests that an oversupply of fat leading to the accumulation of sphingolipids (such as ceramides) in metabolically active tissues may play an important role in the pathophysiology behind β-cell dysfunction and IR in obesity (67). This phenomenon is referred to as "lipotoxicity" (67).

In a minority of GDM cases, less than 10%, β-cell destruction can be due to autoimmunity and the presence of circulating immune markers directed against pancreatic islets (anti–islet cell antibodies) or β-cell antigens (such as glutamic acid decarboxylase [GAD]), also seen in T1D (55, 68). Another minority, around 5%, are thought to be caused by monogenic diabetes with mutations in autosomes, such as in maturity-onset diabetes of the young (MODY), causing abnormalities in the regulation of β–cell mass and/or function (22, 55).

In Table 1, changes in glucose metabolism during normal late pregnancy and GDM are compared.

**Table 1** *Summary of the effects during normal pregnancy and gestational diabetes mellitus on glucose and insulin metabolism (adapted from DiCianni et al, 2003, Lain et al., 2007 and Catalano et al., 1999).*

| | **Normal late pregnancy** | **Gestational diabetes mellitus** |
|---|---|---|
| **Plasma glucose** | Fasting state ↓ | Fasting state ↑ |
| | Postprandial state ↑ | Postprandial state ↑↑ |
| **Insulin secretion** | | |
| *Fasting* | ↑ | ↑ |
| *After glucose load* | | |
| *1st phase* | ↑↑ | ↑ |
| *2nd phase* | ↑↑ | ↑/↑↑ |
| **Insulin resistance** | ↑ | ↑↑ |
| | | |
| **Endogenous glucose production** | ↑ | ↑↑ |
| *(liver)* | | |

## 2.2.2 DIAGNOSTIC CRITERIA AND SCREENING

### *2.2.2.1 International diagnostic criteria and screening*

Before the 1960s, diagnostic thresholds similar to non-pregnant adults were used to diagnose hyperglycemia in pregnancy (39). In 1964, the classical criteria of O'Sullivan and Mahan were published and became a standard for decades to follow (40). Assessing glycemic normality in 752 pregnant women, the risk for developing later T2D was determined, using a 100-g 3-h OGTT. Threshold values of 5.0, 9.2, 8.0, and 6.9 mmol/L at 0, 1, 2, and 3 hours, respectively, representing the mean plus two standard deviations (SD) using the Somogyi-Nelson method for determing glucose in venous whole blood, were defined. Two abnormal values were required for diagnosis. In 1979, the National Diabetes Data group (NDDG) converted the values to approximately 14% higher plasma glucose values (69). Stricter criteria, based on a mathematical conversion of the whole blood glucose values to corresponding glucose oxidase–derived plasma glucose values, were introduced in 1982 by Carpenter and Coustan (70).

In 2008, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study was published with the objectives to evaluate the risk of adverse pregnancy and perinatal outcomes associated with maternal hyperglycemia, less severe than overt diabetes (71). The results of this multicenter study that included 25,500 women who underwent a 75-g 2-h OGTT at 24–32 weeks of gestation showed that the risk for adverse pregnancy and perinatal outcomes was continuous, with no glucose thresholds at which the risk increased. Hence, based on the HAPO study, the IADPSG stated in 2010 that all pregnant women should undergo a 75-g 2-h OGTT universal screening test at 24–28 weeks of gestation, and those at high risk for GDM should be screened for overt diabetes at their first antenatal visit (46). The diagnostic threshold values were set at 1.75 odds ratio (OR) of adverse perinatal outcomes and resulted in values at 5.1, 10.0 and 8.5 mmol/L for fasting, 1-h, and 2-h postprandial glucose values, respectively. One abnormal value was enough to diagnose GDM (46).

The ADA endorsed the new criteria in 2011 (72), the WHO in 2013 (1), the European Board & College of Obstetrics and Gynecology in 2015 (73), and the International Federation of Gynecology and Obstetrics (FIGO) in 2015 (9). However, the increase in prevalence due to lower threshold values gained attention, and research focusing on clinical implications indicated controversies (74, 75). Hence, a universal consensus is still lacking (74, 76), and many of the large diabetes organizations worldwide have formulated their own strategies for detecting GDM, as seen in Table 2.

**Table 2** *Recommended diagnostic and screening criteria for GDM diagnosis in use.*

| Criteria | Approach of testing, glucose load used in OGTT | Screening | Diagnosis (abnormal values required) | Glucose threshold values (mmol/L) | | | |
|---|---|---|---|---|---|---|---|
| | | | | fasting | 1-h | 2-h | 3-h |
| **O'Sullivan and Mahan 1964** | Two-step, 3-h, 100g | None | ≥ 2 | 5.0 | 9.2* | 8.0* *(rounded values)* | 6.9* *(rounded values)* |
| **NDDG 1979** | Two-step, 3-h, 100g | None | ≥ 2 | 5.8 | 10.6 | 9.2 | 8.0 |
| **Carpenter and Coustan 1982** | Two-step, 3-h, 100g | None | ≥ 2 | 5.3 | 10.0 | 8.6 | 7.8 |
| **IADPSG 2010** | One-step, 2-h, 75g | Universal | ≥ 1 | 5.1** | 10.0 | 8.5*** | Not required |
| **WHO 2013** | One-step, 2-h, 75g | Universal | ≥ 1 | 5.1** | 10.0 | 8.5*** | Not required |
| **Finnish current care guidelines 2013** | One-step, 2-h, 75g | Universal except low risk | ≥ 1 | 5.3 | 10.0 | 8.6 | Not required |
| **CDA 2013** | Two-step, 2-h, 75g | Universal | ≥ 2 | 5.3 | 10.6 | 9.0 | Not required |
| **FIGO 2015** | One-step, 2-h, 75g | Universal | ≥ 1 | 5.3 | 10.0 | 8.5 | Not required |
| **NICE 2015** | One-step, 2-h, 75g | Selective | ≥ 1 | 5.6 | Not required | 7.8 | Not required |
| **ACOG 2017 C&C** | Two-step, 3-h, 100g | Universal | ≥ 2 | 5.3 | 10.0 | 8.6 | 7.8 |
| **ACOG 2017 NDDG** | Two-step, 3-h, 100g | Universal | ≥ 2 | 5.8 | 10.6 | 9.2 | 8.0 |
| **ADA 2019** | One-step, 2-h, 75g | Universal | ≥ 1 | 5.1 | 10.0 | 8.5 | Not required |
| **ADA 2019 C&C** | Two-step, 3-h, 100g | Universal | ≥ 2 | 5.3 | 10.0 | 8.6 | 7.8 |
| **ADA 2019 NDDG** | Two-step, 3-h, 100g | Universal | ≥ 2 | 5.8 | 10.6 | 9.2 | 8.0 |

*The threshold values apply to venous plasma unless otherwise specified (* venous whole blood);*
*** fasting plasma glucose values ≥ 7.0mmol/L should be diagnosed as overt diabetes;*
**** 2-h postprandial plasma glucose levels ≥11.1mmol/L should be diagnosed as overt diabetes;*
*OGTT = Oral glucose tolerance test; NDDG = National Diabetes Data Group; IADPSG = International Association of Diabetes and Pregnancy Study Groups; WHO = World Health Organization; FIGO = International Federation of Gynecology and Obstetrics; CDA = Canadian Diabetes Association; NICE = National Institute for Health and Care Excellence; ACOG = American College of Obstetricians and Gynecologists; C&C = Carpenter & Coustan; ADA = American Diabetes Association*

### *Screening*

*Whom?* A universal screening strategy tests all pregnant women, whereas a selective approach is risk factor–based. With a risk factor–based strategy, up to 40% of GDM have been reported to be undetected (77, 78). On the other hand, with a universal strategy, the detection of GDM is more comprehensive, but the clinical importance for detecting milder cases of hyperglycemia is a matter of discussion (79, 80).

*When?* Screening and diagnosis of GDM is usually performed between 24–28 gestational weeks. However, IADPSG and ADA recommend a risk factor–based early screening of high-risk women for pre-existing diabetes at their first antenatal visit using diagnostic thresholds similar to diabetes outside pregnancy (2, 46). Early screening for GDM is a matter of debate, as no larger studies, compared with the HAPO study in late pregnancy (71), have been published to evaluate the diagnostic thresholds with respect to adverse perinatal outcomes based on hyperglycemia in early pregnancy (81, 82).

*How?* In a One-Step Approach, which is more commonly used in Europe, a 2-h 75-g OGTT is applied. One positive result is considered diagnostic (74). In a Two-Step Approach, which is largely used in the USA, a 50-g glucose challenge test (GCT) is performed initially, with a venous glucose measurement one hour later (74). A positive threshold value is considered between 7.2–7.8mmol/L (83). When exceeding the value, a 3-h 100-g OGTT is performed. Two abnormal values are considered diagnostic.

**Table 3** *Different screening strategies for GDM.*

| **WHOM** | | **WHEN** | | **HOW** | |
|---|---|---|---|---|---|
| ***Universal*** | ***Selective*** | ***Early < 24 gw*** | ***Late 24-28 gw*** | ***One-step*** | ***Two-step*** |
| •All pregnant women | •Risk factor-based | •Risk factor-based<br>•Aims to detect overt DM and early GDM<br>•Optimal diagnostic criteria lacking | • Evidence based diagnostic criteria | •2-h 75-g OGTT fasting woman | •50-g GCT with threshold values at 7.2-7.8 mmol/L<br>+<br>•3-h 100-g OGTT |

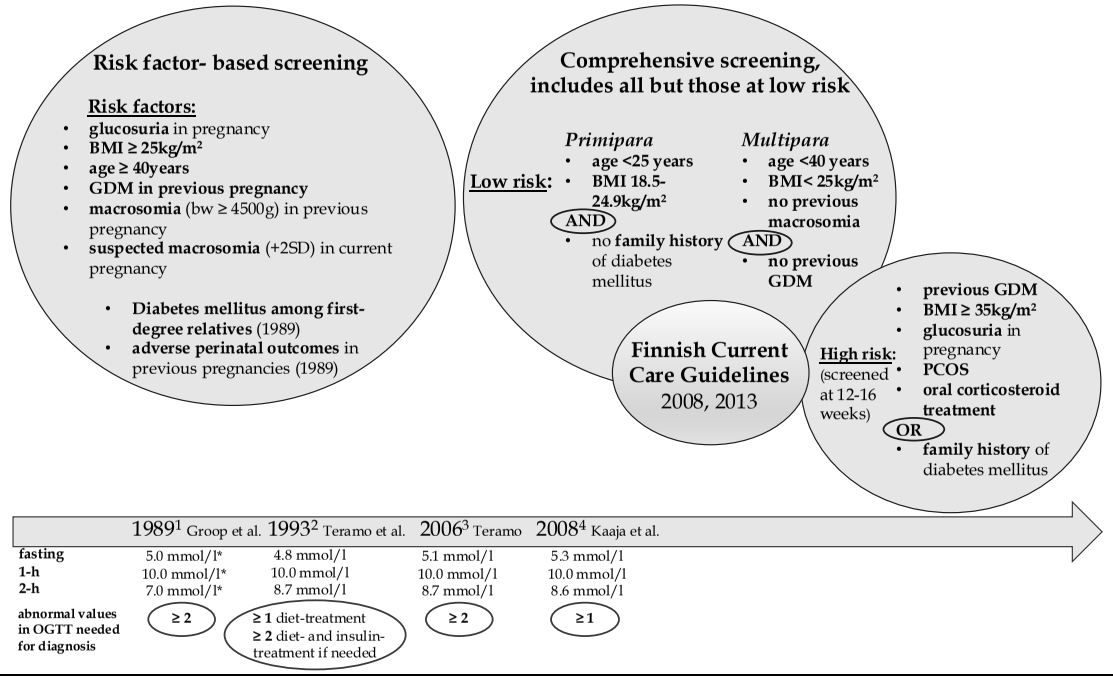
*gw,* gestational weeks; *DM,* diabetes mellitus; *GDM,* gestational diabetes mellitus; *GCT,* glucose challenge test; *OGTT,* oral glucose tolerance test

### *2.2.2.2 Finnish diagnostic criteria and screening*

Figure 2 illustrates the history of screening and diagnosing GDM in Finland. Prior to 2008, screening of GDM was risk factor–based (84, 85). Diagnostic criteria, based on a doctoral thesis from 1991, were specified in an expert statement given in 1993 (84, 86, 87) and updated over time (Figure 2). However, variations on interpretation of the national recommendations existed between hospital districts in the country and were evident (88).

In 2008, the Finnish Medical Society Duodecim published the Current Care Guidelines for GDM, with an updated version in 2013. Today, screening is performed in all pregnant women with the exception of low-risk pregnancies (Figure 2) (22). Diagnosis is based upon a 2-h 75-g OGTT after 12 hours of fasting and performed at 24–28 weeks of gestation with the following thresholds: fasting plasma glucose ≥ 5.3 mmol/L, 1-h postprandial glucose value ≥ 10.0 mmol/L, and 2-h postprandial glucose value ≥ 8.6 mmol/L. In high-risk pregnancies, screening should be performed at gestational weeks 12–16, and if the pregnant woman has tested negative, screening should be repeated at 24–28 weeks (Figure 2) (22). The number of OGTTs performed has doubled since 2008, when the new screening and diagnostic strategies were adopted. The earlier risk factor–based approach in Finland reached 27.5–30% of pregnant women in 2006–2007, compared with 66% in 2018 (unpublished data from the Finnish Institute for Health and Welfare/Medical Birth Register). The Finnish screening percentage can be considered rather high, compared with a European-level estimate of 25–75% in 2016 (89).

**Figure 2** History of screening and diagnostic criteria of gestational diabetes mellitus in Finland.




*BMI*, body mass index; *bw*, birthweight; *GDM*, gestational diabetes mellitus; *PCOS*, polycystic ovary syndrome, *SD*, standard deviation

*[1]Screened at 1st, 2nd, and 3rd trimester, [2]Screened at 26–28 weeks, [3]Screened at 24–28 weeks, [4]Screened at 24–28 weeks, and at 12–16 weeks in case of high-risk pregnancies*

*Threshold values apply for venous plasma samples, unless otherwise indicated (*venous whole blood)*

*References: Groop et al, Aikusityypin diabeteksen hoitosuositus 1989. Suomen diabetesliitto r.y. p. 48-49; Teramo et al., Diabetes ja raskaus. Hoito- ja seurantasuositus. Diabetes, Lääkäriliite 1993. Suomen diabetesliitto r.y., p. 23-26.; Teramo, Raskausdiabetes. In: Diabetes 2006, p. 383-385.; Kaaja et al., Raskausdiabetes 2008. Duodecim 124: p.1556-1569.*

### 2.2.3 PREVALENCE

The global prevalence of hyperglycemia during pregnancy was estimated to be 16% in 2019, of which 84% were due to GDM, according to the International Diabetes Federation (IDF)(10). However, the prevalence of GDM varies greatly, as shown in Table 4. In Finland, the prevalence was 21.3% according to the Finnish Medical Birth Register in 2018 (7).

Global GDM prevalence rates show large variations since diagnostic and screening strategies still vary globally (4). For example, as shown in a European study that estimated a median prevalence of 22.3% in Norway (range 13.0–31.5% using WHO criteria from 1999 (4, 90) and modified IADPSG criteria, respectively) compared with a prevalence of 1.8% in Ireland using the National Institute for Health and Care Excellence (NICE) criteria (21).

Similarly, GDM prevalence also varies depending on studies included in reviews and meta-analyses, since screening and diagnostic criteria have been updated over time and affected prevalence numbers. According to a study from North America in 2002, GDM prevalence increased by 50% when the Carpenter & Coustan criteria were adopted, compared with the previously recommended criteria by the NDDG (91). Similarly, the lower threshold values recommended by the IADPSG in 2010 increased the prevalence of GDM from two- to three-fold, even up to seven-fold, compared with the previous criteria, as reported in a review article published in 2016 (4). For example, in a cohort study from Spain, a 3.5-fold increase in GDM prevalence to 35.5% using the IADPSG criteria was noted in 2014, compared with a prevalence of 10.6% using the Carpenter & Coustan criteria (92).

The importance of recognizing background demographics, ethnic differences, genetic influence and risk factor prevalence (i.e., maternal age, pre-pregnancy adipocity, socioeconomic determinants) when comparing GDM rates is also crucial (4). Even within the same country, GDM prevalence in different study centers may vary by 30–40% (93).

Despite variations in GDM prevalence between countries, it is evident that the prevalence has increased over time, which can not be attributable solely to updated criteria. Increased maternal age, pre-pregnancy BMI, and a higher proportion of pre-gestational impaired glucose tolerance and T2D among women of childbearing age contribute to this phenomenon (3, 8, 9). Likely, the sedentary lifestyle of modern society could be a factor behind the current trend.

**Table 4** *Prevalence (%) of gestational diabetes on a global level (adapted from International Diabetes Federation 2019, Eades et al., 2017, and National medical birth registers from the Nordic countries).*

| **GLOBAL** *(IDF 2019)* | | **EUROPE** *(IDF 2019)* | | **EUROPE** *(Eades et al., 2017)* | | **NORDIC COUNTRIES** *(National medical birth registers 2018)* | |
|---|---|---|---|---|---|---|---|
| Africa | 9.6 | Belgium | 5.1 | Northern | 2.3 | Norway | 5.0 |
| Europe | 16.3 | Croatia | 4.2 | Southern | 9.6 | Sweden | 5.0 |
| North America | 20.8 | France | 8.6 | Western | 7.3 | Finland | 21.3 |
| and Caribbean | | Hungary | 12.5 | | | Denmark | 4.6 |
| South and | 13.5 | Ireland | 11.2 | | | | |
| Central America | | Israel | 10.9 | | | | |
| South East Asia | 27.0 | Netherlands | 27.8 | | | | |
| | | Poland | 9.4 | | | | |
| | | Slovakia | 9.0 | | | | |
| | | Spain | 32.4 | | | | |
| | | Turkey | 17.8 | | | | |
| | | United Kingdom | 20.2 | | | | |

On a local basis, GDM prevalence has been rising in all Nordic countries during the last decade (*Finnish, Swedish, Norwegian, and Danish Medical Birth Registers*). The noticeably higher prevalence in Finland in 2018, compared with the other Nordic countries, can be explained by a more comprehensive screening strategy also encompassing the screening of high-risk women in early pregnancy (22, 94). Additionally, the diagnostic criteria in Finland are more stringent (95). Moreover, in 2018, the mean age at delivery, the proportion of women delivering ≥ 35 years of age, and with a BMI ≥ 30 kg/m$^2$ was highest in Finland (*Finnish, Swedish, Norwegian, and Danish Medical Birth Registers*), as seen in Table 5.

**Table 5** *Maternal data on well-recognized risk factors for GDM in Nordic countries in 2018 (adapted from Finnish, Swedish, Norwegian, and Danish Medical Birth Registers).*

| **Country** | **Mean age at delivery (years)** | | **Age ≥ 35 years (%)** | **BMI ≥ 30 kg/m² (%)** |
|---|---|---|---|---|
| | *Primipara* | *All* | | |
| **Finland** | 29.3 | 31 | 23.6 | 16.3 |
| **Sweden** | 28.8 | 30.5 | 21.8 | 15.4 |
| **Norway** | 28.9 | 30.5 | 20.7 | 8.8 |
| **Denmark** | 29.3 | 30.9 | 20.4 | 3.2 |

*BMI*, body mass index

In Finland, the prevalence rate of GDM has increased from 9.6 to 21.3% in all pregnant women between 2008–2018, based on at least one pathological value in a standard 2-h 75-g OGTT and from 5.7–17.8% according to the ICD-10 code O24.4 for GDM (*unpublished data from the Finnish Institute for Health and Welfare/Medical Birth Register)*. The rate of performed OGTTs during pregnancy doubled during the same timespan from 33.4% to 66.0%, although, the rate of insulin treatment remained at the same level, 2.2–2.5%

of all pregnant women (*unpublished data from the Finnish Institute for Health and Welfare/Medical Birth Register*). The finding indicates that the new criteria for screening and diagnosing GDM since 2008 detect more of mild GDM cases.

Noteably, the dramatic rise in GDM prevalence in Finland also parallels the increased prevalence of widely accepted risk factors. During 2010–2019, the age of primiparas in Finland increased from 28.1–29.5 years and the rate of obese pregnant women (BMI>30 kg/m$^2$) from 12 to 17% (7). Of all pregnant women above 35 years of age, 28% had a pathological OGTT result in 2018 (http://urn.fi/URN:NBN:fi-fe2019121948893).

## 2.2.4 CONSEQUENCES AND COMPLICATIONS OF HYPERGLYCEMIA DURING PREGNANCY

### *2.2.4.1 Short-term complications*

#### 2.2.4.1.1 Obstetrical outcomes and consequences for the mother

The HAPO study in 2008 showed that the adverse effects of hyperglycemia during pregnancy had no specific threshold, rather, appeared to be continuously associated with glucose levels, even below those, diagnostic for diabetes mellitus (71). The finding was verified in a meta-analysis by Farrar and colleagues in 2016 (12).

GDM increases risks for pre-eclampsia, primary cesarean delivery, preterm deliveries (<37 gw), and pelvic birth injuries (71), largely because of neonatal macrosomia (11, 75, 96-98). Additionally, a higher prevalence of polyhydramnios and gestational hypertension is reported in pregnancies complicated by hyperglycemia and GDM (97, 99), as well as induction of labor and instrumental deliveries (12).

Combined with obesity, the effects on adverse obstetric outcomes have an additive effect, since obesity alone is an independent risk factor for poor obstetric outcomes (100). Further, ante- and perinatal depressive symptoms (101, 102) , and puerperal depression (103, 104), have in some studies been reported more often among women with GDM. However, other studies report depression to precede, rather than to follow, the diagnosis of GDM (105). The association is nevertheless important, as it increases the risk of a post-partum depression syndrome, with adverse effects for both the mother and her child (103).

#### 2.2.4.1.2 Perinatal and neonatal outcomes

*Fetal growth and macrosomia*

Fetal growth is a delicate, complex and multifactorial process influenced by genetics, the intrauterine milieu and metabolism, and maternal, fetal and placental factors (106-108). Only a few of the factors will be discussed in greater detail, with a focus on glucose metabolism.

In 1952, an epidemiologist who primarily cared for pregnant women with T1D, Jørgen Pedersen from Denmark, defended his doctoral thesis on diabetes and pregnancy (38). He suggested that fetal overgrowth was a result of increased transplacental transfer of glucose as a consequence of hyperglycemia in the pregnant woman, resulting in subsequent hyperglycemia in the fetus, who would respond with hyperinsulinemia caused by increased insulin secretion by the fetal β-cells. This would lead to a greater fetal utilization of glucose and subsequent macrosomia. The theory behind this phenomenon is called Pedersen's hypothesis (Figure 3), and it has been widely accepted that fetal insulin is a primary growth factor in utero (109), and that extra glucose in the fetus will be stored as adipose tissue (11).

However, the rising prevalence of obesity and the different pathophysiology behind T1D and GDM led research to explore additional explanations behind the pathophysiology of fetal macrosomia. Newborns to obese GDM women with an optimal glucose balance can also be macrosomic (109), and obesity alone increases risk for macrosomia (100). Hence, evidence suggests that maternal lipid metabolism, more explicitly, the free fatty acids and the inflammatory milieu of pregnancy in obese women with increased IR may also contribute to macrosomia (109). In order to further understand the complexity of fetal growth, the importance of the placenta and the metabolic milieu of early pregnancy has emerged as important areas of research (110-112).

The definition of macrosomia varies in the literature (113, 114). According to the national guidelines for GDM in Finland since 2013, the definition for macrosomia or large for gestational age (LGA) is a birthweight of + 2 SD (≥ 97.5th percentile) according to gestational age and sex (22). In the previous guideline, published in 2008, an offspring birthweight of ≥ 4500g independent of gestational age was also defined as macrosomia (115). In a Finnish retrospective cohort study encompassing 27,000 singleton pregnancies, 3.4% of the newborns had a birthweight > 4500g, compared with 8.2% in women diagnosed with gestational diabetes (113). In another recent Finnish study among 4033 women that evaluated perinatal outcomes depending on

diagnostic criteria used, the proportion of LGA infants (defined as +2 SD) was 2.7% in non-GDM women, 2.7% in women with treated GDM according to IAPSDG criteria, and 4.2% according to NICE criteria (116).

Although fetal macrosomia is a typical complication, GDM pregnancies can also be affected by fetal growth restriction. GDM is associated with an increased risk for hypertensive disorders of pregnancy (i.e., chronic hypertension, gestational hypertension or pre-eclampsia), which may predispose to placental insuffiency (117). Also, severe hyperglycemia during early pregnancy is thought to cause microvascular damage and, thus, lead to placental dysfunction resulting in intra-uterine growth restriction (13). Further, an excessively strict diet may lead to a gestational weight gain below recommendations and affect fetal growth negatively (118).

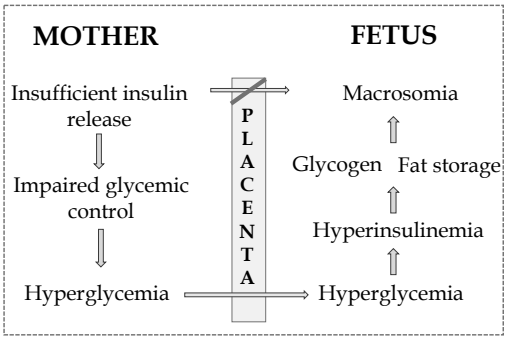



**Figure 3** Modified Pedersen's hypothesis illustrating the pathophysiology behind offspring macrosomia as a consequence of maternal hyperglycemia during pregnancy. Redrawn with modifications and permission from Kc et al., Gestational Diabetes Mellitus and Macrosomia: A Literature Review. Ann Nutr Metab 2015;66(suppl 2):14-20. S. Karger AG, Basel.

*Other complications*

Shoulder dystocia, clavicle fractures and brachial plexus injuries (Erb's palsy) of the newborn are rare but severe complications of GDM and fetal macrosomia, which are more pronounced in a vaginal birth (11, 22). Additionally, admissions to the neonatal intensive care unit due to neonatal hypoglycemia, respiratory distress syndrome, hyperbilirubinemia, premature delivery and low Apgar scores are more common in GDM offspring (9, 11, 65, 71). Moreover, an increased risk for malformations and fetal distress have been reported (65, 75). Further, undiagnosed GDM increases risk for late stillbirths (65, 119), but the risk for perinatal mortality is controversial (65, 75, 96). The risk for adverse perinatal outcomes is, in general, increased in cases of undiagnosed pregestational diabetes or GDM requiring insulin treatment (96).

### *2.2.4.2 Long-term complications*

#### 2.2.4.2.1 The mother

*Type 2 diabetes*

Estimates of the risk for developing T2D after GDM vary between 3–70% (15, 120). Possible explanations for the large variations in these estimates are differences in diagnosing GDM, genetic influence, and length of follow-up (4, 15). In 2009, Bellamy and colleagues published a rigid meta-analysis encompassing 32,000 women with GDM of any parity or ethnic origin, with a follow-up time ranging between the included studies from 6 weeks to 28 years postpartum. They found a seven-fold risk for developing T2D over time when compared with normoglycemic women (17). A recent meta-analysis reported a nearly 10-fold higher overall risk for T2D in women with a history of GDM (121). The risk seems to increase with progressing degree of glycemic abnormality during pregnancy (122), advancing age, increasing BMI, an early diagnosis of GDM, insulin treatment, recurrent GDM, and elevated fasting glucose levels (123-125). Findings of candidate genes and increased frequency of alleles associated with a greater risk for T2D in women with a history of GDM have been reported (126, 127). Further, variations in β-cell function, degree of metabolic stress and retained adiposity posed by pregnancy, as well as post-partum behaviors all contribute to the individual risk for later T2D (128).

*Metabolic syndrome*

GDM, as well as milder hyperglycemia, has been linked to a nearly four-fold risk for metabolic syndrome (129-131), especially in Caucasian women and those women with higher BMI (129). However, an increased risk for metabolic syndrome in non-obese women with a history of GDM has also been reported (132). Elevated fasting plasma glucose values and two abnormal glucose values in OGTT seem to predict the greatest risk for later metabolic syndrome (133). Metabolic syndrome, characterized by visceral obesity, dyslipidemia, hypertension and insulin resistance, is a risk factor for cardiovascular diseases and T2D (129, 134), and shares many common features with GDM (129).

*Cardiovascular diseases*

A recent large cohort study from the United Kingdom, reported an almost three-fold risk for ischemic heart diseases in women with a history of GDM (135). Similarly, in a Canadian study, women with a history of GDM had a 70% increased risk for cardiovascular disease, although much of this risk was

attributable to development of diabetes (14). However, two recent meta-analyses showed a two-fold increase for cardiovascular disease after GDM (136, 137), independent of T2D, indicating that women with a history of GDM also solely comprise an at-risk population for cardiovascular events (137). Additionally, milder degrees of glucose intolerance increase risk for cardiovascular diseases (138). Subsequent weight gain, unhealthy lifestyle (139), and subclinical atherosclerosis in GDM pregnancies all contribute to the elevated risk (140).

#### 2.2.4.2.2 The offspring

*The Developmental Origins of Health and Disease (DOHaD)*

The idea that the intrauterine environment could have long-standing consequences in later life was first postulated 40 years ago. In 1980, Freinkel in Chicago highlighted the importance of the metabolic milieu of the fetus, as well as the potential permanent changes or harms in the offspring due to an excess of fuels – or "fuel mediated teratology" – from behavioral, anthropometric and metabolic perspectives (141).

Likewise, later in the 1980s, Barker in England published a series from different parts of England indicating that areas with high perinatal mortality, at that time mostly due to low birthweight, showed an increased risk for adult cardiovascular mortality (142, 143). The theory of Barker also indicated that the environment of early life in utero could have long-spanning effects on adult disease burden. This formed the basis of the developmental origins of adult health and disease hypothesis (DOHaD) (19, 142). The hypothesis emphasizes developmental plasticity, early changes and responses in the organs under influence of the hormonal and nutritional state of pregnancy, epigenetic mechanisms and glucocorticoids during critical periods of early fetal development (142), since findings of a direct genetic link are sparse (18, 144, 145).

*Abnormal glucose metabolism*

Offspring born to GDM mothers have an increased risk for abnormal glucose metabolism and T2D in adolescence and adulthood (15, 146-149). A HAPO follow-up study published in 2019 demonstrates a linear relationship between maternal glucose levels during pregnancy and risk for abnormal glucose tolerance in the offspring aged 10–14 years (16). Although maternal obesity has been regarded as a mediator between the association, a recent review showed the association to be independent of maternal BMI (146).

Fetal hyperglycemia can lead to modifications of fetal islet cells that could lead to abnormal islet function in adulthood (141). Additionally, epigenetic changes induced by maternal hyperglycemia seem to play a role (148). However, the impact of shared genetic traits is difficult to rule out, as well as the influences of postnatal lifestyle-related factors (13). In a recent study, fetal exposure to maternal diabetes (GDM or T1D) increased skeletal muscle expression of specific micro RNAs that affects insulin sensitivity and secretion in the offspring. The finding might further explain the increased insulin resistance detected in the offspring (150).

*Overweight, obesity and metabolic syndrome*

An increased risk for childhood overweight and obesity has been reported in offspring exposed to maternal hyperglycemia in utero (15). The confounding effect of maternal overweight is a matter of debate since the association between maternal GDM and offspring overweight has been significantly attenuated when controlling for maternal pre-pregnancy BMI (15, 151-153). In a Finnish birth cohort study evaluating overweight and abdominal obesity at 16 years of age in offspring born to GDM women, offspring with the greatest risk for overweight were those born to women with concomitant obesity and GDM. Maternal obesity increased the risk, but GDM solely had only a small impact (154). However, the risk for metabolic syndrome in adolescence and adulthood in GDM offspring seem to be increased, especially in offspring born LGA (13).

*Other consequences*

At early stages of research, some studies have indicated that maternal hyperglycemia during pregnancy can affect the cognitive abilities of the offspring. A meta-analysis identified infants born to diabetic mothers to have an increased risk for cognitive impairment during their first year, which could lead to certain delays in mental performance later (155). However, the heterogenity among studies was wide and many studies had not distinguished between the type of maternal diabetes. A possible explanation behind the phenomenon is proposed through fluctuating concentrations of glucose in utero, and potential ketonemia (156, 157). Opposite findings have also been reported (158), suggesting the association between GDM and offspring neurocognitive development to be more from shared environmental and genetic factors.

### 2.2.5 RISK FACTORS FOR GESTATIONAL DIABETES MELLITUS

In this thesis, according to the perspective of the author, the risk factors for GDM are divided into two separate categories, as seen in Table 6. The traditional risk factors are defined as those comprehensively studied, well-accepted and widely discussed in the literature, in contrast to the non-traditional ones, which have been studied either with respect to T2D only or inadequately and/or with conflicting results in relation to GDM.

**Table 6** *Risk factors for gestational diabetes mellitus (adopted from Ben-Haroush et al. 2003, Dode et al. 2009, NICE guideline 2015 Diabetes in pregnancy, Käypä Hoito Suositus 2013 Raskausdiabetes).*

| Traditional risk factors | Non-traditional risk factors |
|---|---|
| Advanced age | Multiparity |
| Increased BMI | Socioeconomic factors |
| Increased pre-pregnancy weight | Smoking |
| Family history of diabetes | Low birthweight |
| Family or personal history of GDM | High intake of saturated fat |
| Macrosomia | Short stature |
| Ethnic family origin with high prevalence of diabetes | Gestational weight gain |
| | Physical inactivity |
| Polycystic ovary syndrome | Pregnancy-induced hypertension |
| Oral glucocorticoid treatment | |
| Glucosuria in pregnancy | |

*BMI*, body mass index; *GDM*, gestational diabetes mellitus

#### *2.2.5.1 Traditional risk factors*

The most acknowledged risk factors for GDM are an increased maternal pre-pregnancy BMI, advanced maternal age, a family history of diabetes mellitus, a personal history of GDM or a macrosomia infant, and an ethnicity with high prevalence of diabetes (20, 22, 125, 159, 160). These factors will be discussed, as these are often those highlighted in risk factor–based screenings (21, 161, 162). Further, excessive gestational weight gain, multiparity, glucosuria in early pregnancy, polycystic ovary syndrome (PCOS), are well-recognized risk factors for GDM as well (22, 125, 163).

*Pre-pregnancy BMI*

Torloni and colleagues showed in 2009 that the odds ratio (OR) for GDM among overweight women (BMI 25–29 kg/m$^2$) was two-fold higher compared

to normal weight women (BMI 20–25kg/m$^2$), and three- to almost six-fold higher for obese (BMI 30–34 kg/m$^2$) and morbidly obese women (BMI > 35 kg/m$^2$) (164). Similarly, in 2019 a meta-analysis showed a strong positive association between pre-pregnancy BMI and GDM (165). A low BMI, compared to normal BMI, had a protective effect (165). Excessive adipose tissue releases unsaturated fatty acids, glycerol, hormones and proinflammatory cytokines, which all exacerbate insulin resistance and negatively affect insulin secretion through β-cell dysfunction (166).

*Advanced maternal age*

A recent meta-analysis, encompassing 120 million women, showed a linear relationship between increasing age and GDM. For each one-year increase in age from 18 years GDM risk for the overall population increased by 8%, being highest in the group of Asian, compared with European women (167). Similarly, the OR for developing GDM was six times higher in women 35–39 years, and 8 times higher in women > 40 years compared with women < 20 years (167). Chronic low-grade inflammation that increases with age and further pronounces insulin resistance might partially explain the findings (168).

*A family history of diabetes*

A family history of diabetes mellitus has, in a recent meta-analysis, been reported to be a significant risk factor for GDM (169). It is difficult to exclude the effects of an inherited lifestyle and obesity, however, T2D and GDM share a common pathophysiology in terms of an increased insulin resistance and insufficient insulin secretion. Further, a number of shared alleles between T2D and GDM controlling for β-cell function and insulin sensitivity have been identified (127).

*Prior GDM and/or a history of fetal macrosomia*

Prior GDM was reported as the most powerful risk factor for GDM in a meta-analysis from 2018 conducted among Asian studies (170). Moreover, a history of fetal macrosomia in a previous pregnancy is reported to increase the risk for recurrent GDM (170-172). Insulin treatment, diagnosis of GDM in early pregnancy and poor glycemic control are all predictive factors for recurrent GDM (172), as well as for fetal macrosomia (173, 174).

*Ethnicity*

An ethnicity with high prevalence of diabetes increases risk for GDM (125). Commonly, a non-Caucasian ethnicity is considered at risk, with Africans, Indians, South Asians and women from the Middle East at greatest risk (22, 175). In a large cohort from the USA, non-Hispanic whites born in the USA were considered to have the lowest risk, whereas, Indians born outside the USA were considered to be at highest risk (175). Various factors are thought to explain the differencies across ethnic groups, such as different diagnostic and screening strategies, differences in body composition and genetic factors (176). Migration to foreign countries also causes lifestyle changes in diet and behavior, possible predisposing for metabolic stress and the development of GDM in immigrants (175).

#### *2.2.5.2 Non-traditional risk factors*

Multiparity, physical inactivity, gestational weight gain, maternal short stature, maternal low or high birthweight, smoking, and socioeconomic factors can all be regarded as non-traditional risk factors for GDM (177). Further, adverse dietary habits, alfa thalassemia trait, a multiple pregnancy, a history of congenital malformations, an early age of menarche (178), vitamin D deficiency (179), pregnancy-induced hypertension and preeclampsia, and increased iron stores have been reported, although studied less, as risk factors (125). Of these, the non-traditional risk factors included in the studies of the thesis will be described in greater detail.

*Maternal short stature*

An individual's height has, in several previous studies, emerged as an important indicator of health (180), with a short stature, in particular, being a potential risk for non-communicable diseases. A meta-analysis published in 2012 showed a short stature in women to increase the risk for T2D (181). Similarly, in non-diabetic, non-pregnant individuals, taller people tend to have lower post-prandial glucose levels compared with shorter people, with no differences in fasting glucose concentrations, using a standard OGTT (182-184). Tall individuals also tend to have a reduced risk for cardiovascular events (185), as well as for strokes (186).

As shown in Table 7, maternal short stature has been rather uniformly inversely associated with GDM (187-190), although some individual studies have reported no differences in stature between GDM and non-GDM women (191). However, a meta-analysis published in 2019, reported each 5 cm

increase in height to reduce the risk for GDM by 20%, independently of ethnic origin (23) (Table 8).

There are several hypotheses trying to explain the association between maternal short stature and GDM. Taller people have proportionally more metabolically active muscle tissue, which is known to be the major tissue for glucose metabolism (183). Thus, taller people, compared with short ones, have a larger amount of metabolically active muscle tissue to metabolize the same fixed amount of glucose given in a standard OGTT (183). Further, height has been positively associated with pancreatic β-cell function and insulin sensitivity (192). Birth size is also positively associated with adult height (193), and short stature might result from non-optimal prenatal growth or early malnutrition that can lead to impaired glucose regulation in adulthood, predisposing to T2D (194). Moreover, short stature is associated with adiposity (195), whereby exclusion of obesity as a mediator between short stature and GDM is difficult. Low socioeconomic status is also associated with both short stature as well as GDM (23, 196). Finally, combined alleles for both short stature and risk for T2D have been identified (197).

**Table 7** *Reference list of publications assessing the relationship between maternal height and gestational diabetes mellitus.*

| Reference | Country | N | Maternal height, method assessed | Association between risk factor and GDM | Prevalence of GDM |
|---|---|---|---|---|---|
| *Jang et al., 1998* | South Korea<br>1991-1994 | 9 005 | Comparisons of avarage<br>height between groups according to<br>I: negative screen, positive screen + negative OGTT,<br>postive OGTT<br>II: ≤157cm, 159, 162, ≥163cm | Negative | 1.9% |
| *Anastasiou et al., 1998* | Greece<br>1990-1996 | 2 772 | Comparisons of avarage<br>maternal height between groups according<br>to glucose abnormality:<br>Normal, one abnormal glucose value,<br>GDM, T2D, T1D | Negative | 24.7% |
| *Branchstein et al., 2000* | Brazil<br>1991-1994 | 5 664 | 136-151cm, 151.1-155.4cm,<br>155.5-159.8cm, 160.0-183.4cm | Negative | Not reported |
| *Tabak et al., 2002* | Hungary<br>1999-2000 (1.cohort)<br>1985-1990 (2. cohort) | 1 635 (1. cohort)<br>186 (2. cohort) | Maternal height, comparisons of avarage<br>maternal height between GDM and healthy<br>controls | Neutral | 5.7% |
| *Rudra et al., 2006* | United States of America<br>1996-2002 | 1 644 | <160cm, 161–165cm,<br>166–170cm, >170 cm. | Negative | 4.1% |
| *Ogonowski et al., 2010* | Poland<br>2000-2007 | 1 830 women with abnormal<br>glucose challenge test<br>1 011 healthy women | Comparison of mean height<br>between mothers with and without GDM | Negative | - |
| *Brite et al., 2014* | United States of America<br>2002-2008 | 135 861 (cohort)<br>15 761 GDM (meta-analysis)<br>205 828 non-GDM (meta-analysis) | 101–157.5cm, 157.6–162.6cm<br>162.67–167.6cm, 167.98–210.0cm | Negative | Cohort 4.1% |
| *Laine et al., 2018* | Finland<br>2009-2015 | 5 223 | Maternal height, comparisons between groups<br>according to maternal height level<br>12.5%, 25%, 25%, 25%, and 12.5% of the total distribution.<br>I < 159 cm, II 159-163 cm, III 164-167 cm,<br>IV 168-172 cm, V > 172 cm | Negative | According to height groups:<br>group I: 28.7% (highest)<br>group III: 19.9% (lowest) |
| *Li et al., 2018* | China<br>2012-2014 | 6 941 | Comparisons between groups<br>according to maternal height level (≤158.0 cm,<br>158.1–161.0 cm, 161.1–164.0 cm, and >164.0 cm) | Negative | 14.7% |
| *Mendoza et al., 2018* | Multicenter study<br>in Europe<br>(Time frame not reported) | 984 | Maternal height, comparisons between groups<br>according to maternal height level<br><163 cm, 163-169cm, >169cm | Negative | 43.8%<br>(<20gw 27.9%,<br>24-28 gw 15.5%,<br>35-37gw 15.2%) |
| *Marshall et al., 2019* | USA<br>2007-2010 | 1 775 984 | Comparisons of GDM prevalence between<br>groups according to avarage height within the cohort<br>≤ 20th percentile (short height), ≥ 80th percentile (tall height)<br>21st-79th%ile for height (avarage height) = reference group | Negative | Not reported |

*GDM*, gestational diabetes mellitus; *gw*, gestational weeks; *OGTT*, oral glucose tolerance test; *T1D*, type 1 diabetes; *T2D*, type 2 diabetes

**Table 8** *Meta-analysis assessing the relationship between maternal height and gestational diabetes mellitus.*

| Reference | Country | Inclusion criteria | Exclusion criteria | Studies | Women included | Pooled OR of maternal height and GDM |
|---|---|---|---|---|---|---|
| *Arafa et al., 2019* | Italy | Conducted in humans<br>OR or RR with their 95% CI between maternal height and GDM provided | Risk estimates were unavailable | 10 | 126 094 | 20% reduction in risk of GDM/ 5cm increase in height [pooled OR = 0.80, (95% CI 0.76, 0.85) |

*CI*, confidence interval; *GDM*, gestational diabetes mellitus; *OR*, odds ratio; *RR*, relative risk

*Maternal low birthweight*

The association between low birthweight and increased risk for cardiovascular diseases (198), hypertension, metabolic syndrome and T2D (199) is well recognized. David Barker showed a positive relationship between neonatal/postnatal mortality and adult mortality due to ischemic heart diseases (143-145). These conditions were associated with poor living standards and indicated that a poor nutritional state in early life could predispose to adverse effects of an affluent diet later on (143). After the proposal of the "thrifty phenotype" hypothesis to determine an individual's later risk for T2D and other metabolic diseases, the importance of adequate organ development in both structure and function through a sufficient and healthy maternal nutritional state during pregnancy has become an important target for prevention of future adult morbidity (145).

The inverse relationship between low maternal birthweight and development of T2D is established (194, 200), although some studies also indicate the relationship to be U-shaped (201). The link between birthweight and GDM is rather conflicting, as shown in Table 9. Some studies have demonstrated an inverse (202-206), and some studies a U-shaped, relationship (207-210). A recent Danish study reported an inverse relationship between maternal ponderal index and GDM (211).

A low birthweight has been linked to IR (212) and impaired glucose tolerance in adulthood due to impaired endocrine pancreatic development, resulting in impaired β-cell function (199). Nonetheless, insulin is considered an important growth hormone and a few studies indicate that there could be a genetic association through certain risk alleles predisposing both to impaired insulin secretion and reduced fetal growth (213).

**Table 9** *Reference list of publications assessing the relationship between maternal birthweight and gestational diabetes mellitus.*

| Reference | Country | N | Maternal birthweight, method assessed | Association between maternal birthweight and GDM | Prevalence of GDM |
|---|---|---|---|---|---|
| ***Williams et al., 1999*** | United States of America<br>1987-1995 | 41 839<br>21 528 *non-Hispanics*<br>6 359 *African-Americans*<br>7 456 *Native Americans*<br>6 496 *Hispanics* | < 2000g, 2000-2499g, 2500-2999g,<br>3000-3999g, > 4000g<br>(maternal birth certificates) | Negative (non-Hispanics,<br>Native American, Hispanics)<br>U-shaped (African-American) | 2.8% non-Hispanics<br>2.6% African-Americans<br>2.7% Native Americans<br>3.0% Hispanics |
| ***Egeland et al., 2002*** | Norway<br>1988-1998 | 138 714 | <2500g, 2500-2999g, 3000-3499g,<br>3500-3999 g, 4000-4500g, >4500g<br>(medical records) | Negative | <20 years: 1.5/1000 deliveries<br>>30years: 4.2/1000 deliveries |
| ***Innes et al., 2002*** | United States of America<br>1994-1998 | 440 women with GDM (cases)<br>22 955 remaining women with no GDM (controls) | <2000g, 2000-2499g, 2500-2999g,<br>3000-3499, 3500-3999, ≥4000g<br>(maternal birth certificate) | crude + adj (gest age): U-shaped<br>adj (BMI, maternal dm)<br>Negative | Not reported |
| ***Seghieri et al., 2002*** | Italy<br>1999-2001 | 604 | <10th percentile, >10th percentile<br>(self-reported and from written medical records) | Negative | 23.5% |
| ***Savona-Ventura et al., 2003*** | Malta<br>1996-2001 | 162 women with GDM<br>250 controls | 1000-2000g, 2000-2500g, 2500-4000g<br>4000-4500g, >4500g<br>(medical records) | U-shaped | Not reported |
| ***Claesson et al., 2007*** | Sweden<br>1973-1983 | 421 women with GDM<br>60 890 controls | <2500 vs ≥2500g, <4500g vs ≥4500g<br>Birthweight deviation (SD) <-2, ≥2- <-1,<br>≥-1-<1, ≥1- <2, ≥2 (medical records) | U-shaped | Not reported |
| ***Yeung et al., 2010*** | United States of America<br>1989-2001 | 21 647 | <2.5 kg, 2.5–3.1kg, 3.2–3.8kg,<br>3.9–4.4kg, or ≥4.5kg<br>(self-reported) | Negative | 6.4% |
| ***Rogvi et al., 2011*** | Denmark<br>1989-2007 | 84 219 (mothers born 1974–1977)<br>32 376 (mothers born 1978–1981) | Birthweight by gestational age (z-score)<br>(medical records) | U-shaped | 1. cohort: 1.1 % by GDM<br>2. cohort: 0.8 % by GDM |
| ***Ogonowski et al., 2012*** | Poland<br>2000-2007 | 787 GDM pregnancies<br>801 healthy pregnancies | <2500g, 2500-2999g, 3000-3499g,<br>3500-3999g, ≥4000g<br>(medical records) | Negative | Not reported |
| ***Su et al., 2016*** | China<br>2013 | 5 479 | ⩽2500 g, 2500 to 2999 g,<br>3000 to 3499 g, 3500 to 3999 g, ⩾4000 g<br>(medical records) | Negative | 20.8% |
| ***Zhu et al., 2017*** | China<br>2013 | 15 194 | 0-1999g, 2000-2499 g,<br>2500-2999g, 3000-3499g, 3500-3999g,<br>≥4000g<br>(questionnaires) | Negative | 19.7% |

*BMI,* body mass index; *DM,* diabetes mellitus; *GDM*, gestational diabetes mellitus; *SD*, standard deviation

*Smoking during pregnancy*

Smoking is the most important preventable cause of death and cardiovascular disease globally (214, 215). With both prothrombotic and atherogenic effects it increases and acts synergistically with other risk factors on many cardiovascular diseases (214). The WHO has also newly endorsed smoking as a modifiable risk factor for T2D (216). The positive association between smoking and T2D has been verified in two recent systematic reviews (217, 218).

However, the relationship between smoking and GDM still remains controversial, as reported in Table 10. Several epidemiological studies have assessed the relationship and positive (219-222), negative (26, 223), as well as neutral (27, 224, 225) associations have been reported. No association between smoking and GDM was detected in a systematic review from 2008 (24), however, the number of available studies was low and the available ones were mostly based on unadjusted models (24) (Table 11). However, in 2018, a meta-analysis reported the same finding (25) (Table 11).

Cigarette smoking influences glucose homeostasis as it increases IR, both through a direct effect on insulin-mediated glucose uptake, as well as on pancreatic β-cell function and insulin secretion (218). Likewise, higher fasting glucagon levels have been reported among non-pregnant heavy smokers (226), and glucagon increases IR and the risk for T2D (227). Also, changes in body composition and adverse fat distribution have been reported among smokers (218). In smoking pregnant women with GDM, fasting glucose concentrations have been reported to be unaffected (228) or elevated (229), 1-h postprandial concentrations to be higher (228, 229), 2-h postprandial concentrations to be unaffected and 3-h postprandial concentrations to be lower (228, 229). The immediate effects on glucose homeostasis and elevated postprandial glucose concentration may be a result of an accelerated gastric emptying and increased glucose absorption detected in smokers (230, 231). However, an opposite idea of a reduced gastric emptying that could explain the lower 2-h and 3-h concentrations reported in other studies has also been proposed (226).

**Table 10** *Reference list of publications assessing the relationship between smoking during pregnancy and gestational diabetes mellitus.*

| Reference | Country | N | Smoking status, method assessed | Association between smoking during pregnancy and GDM | Prevalence of GDM |
|---|---|---|---|---|---|
| *Solomon et al., 1997* | United States of America<br>1989-1994 | 5 259 | Never, past, or current;<br>Number of cigarettes smoked/day<br>(self-reported) | Positive for<br>current smokers | 4.9% |
| *Zaren et al., 2000* | Sweden | 499 | Average number of cigarettes smoked/day<br>(self-reported) | Positive | Not reported |
| *Innes et al., 2002* | United States of America<br>1994-1998 | 440 cases,<br>22 955 controls | Smoking during pregnancy (yes/no)<br>(medical records) | Neutral | Not reported |
| *Terry et al., 2003* | Sweden<br>1987-1995<br>Two consecutive pregnancies | 212 190 | Nonsmokers, light smokers (1-9 cigarettes/day), and moderate-to-heavy smokers (≥10 cigarettes/day)<br>(self-reported) | Neutral | 0.4% (1. pregnancy)<br>0.6% (2. pregnancy) |
| *England et al., 2004* | United States of America<br>1992-1995 | 4 289 | Average number of cigarettes smoked/day<br>current, as well as history of smoking status<br>(self-reported) | Positive | 2.4% |
| *Anna et al., 2008* | Australia<br>1995-2005 | 950 747 | Average number of cigarettes smoked/day<br>(medical records) | Neutral | 4.4'% |
| *Roelands et al., 2009* | United States of America<br>2000-2004 | 21 207 981 pregnancy- and delivery-related codes,<br>640 813 included ICD-9<br>codes for smoking | ICD-9: smoking 305.1 (tobacco use disorder, excludes smoking complicating pregnancy) and V15.82 (history of tobacco use) | Negative | Not reported |
| *Haskins et al., 2010* | Puerto Rico<br>2000-2003 | 1 006 | Average number of cigarettes smoked/day<br>before and during pregnancy (self-reported) | Neutral | 11.8%<br>(abnormal glucose tolerance) |
| *Hosler et al., 2011* | United States of America<br>2004-2006 | 2 854 | Non-smoker, abstainer, smoker (self-reported)<br>Second-hand smoke exposure (self-reported) | Neutral | 0.4% (1. pregnancy),<br>0.6% (2. pregnancy) |
| *Simas et al., 2014* | United States of America<br>2007-2011 | 3 029 | Average number of cigarettes smoked/day<br>(self-reported) | Neutral | 4.7% |
| *Zhang et al., 2014* | United States of America<br>1989-2001 | 14 437 | Never, former, or current smoker<br>(self-reported) | Positive for<br>current smokers | Not reported |
| *Collier et al., 2017* | Scotland<br>1981-2012 | 1 891 097 | Yes/no or not known<br>(self-reported) | Negative | 1.9% |
| *Konstantakou et al., 2019* | Greece<br>2000-2015 | 7 437 | Non-smokers (A), those who ceased smoking at pregnancy (B), and smokers (C) | Neutral | 33.4% |

*GDM,* gestational diabetes mellitus

**Table 11** *Meta-analyses assessing the relationship between smoking during pregnancy and gestational diabetes mellitus.*

| Reference | Country | Inclusion criteria | Exclusion criteria | Studies | Women included | Pooled OR of smoking during pregnancy for GDM |
|---|---|---|---|---|---|---|
| *Wendland et al., 2008* | Brazil, Argentina | Association between smoking during pregnancy and GDM<br>Studies providing adjusted or crude RR or OR<br>Diagnosis of GDM based on OGTT or clinical diagnosis | Type 1 diabetes,<br>Reports of tobacco products other than cigarettes<br>Animal studies<br>Smoking outside pregnancy | 12 studies | Not reported | Crude<br>1.03 (99% CI 0.85–1.25)<br><br>4 studies with adjusted models<br>0.95 (99% CI 0.85–1.07) |
| *Wang et al., 2018* | China | Association between smoking during pregnancy and GDM<br>Studies providing OR with 95% CI for highest versus lowest level of smoking<br>Reference group of non-smokers | Review studies<br>Non-English studies<br>Studies not providing primary or adjusted data | 12 studies | 1 364 468 | 0.98 (95% CI: 0.88–1.10) |

*CI*, confidence interval; *GDM*, gestational diabetes mellitus; *OGTT*, oral glucose tolerance test; *OR*, odds ratio, *RR*, relative risk

*Maternal socioeconomic status*

SES refers to social and economic factors that can be assessed in different manners, and different indicators might represent different stages of life (232). The most used indicators for SES are personal/family household income, education level, occupation (233), and area of living/postal code (26, 27).

An individual´s SES affects a person´s health in general and a higher SES, assessed as educational attainment (234) and/or higher level of income (235), is generally linked to better health outcomes. Explicitly, the level of family income is inversely associated with many non-communicable diseases such as coronary heart disease, hypertension and diabetes (235). Additionally, there is a negative association between a lower SES and T2D (236).

However, studies assessing the relationship between maternal SES and GDM are conflicting. As summarized in Table 12 and 13, some studies indicate an inverse relationship, assessed as income (237, 238) or area of living (26, 27), and some studies indicate a neutral relationship, assessed as area of living (29, 30), income (29, 239), or educational attainment (29, 240). Also, an inverse relationship between maternal educational attainment and GDM has been reported (28, 241), and overweight and obesity seem to be the most important mediators (241). A recent Chinese study reported educational attainment to be inversely associated with GDM, and the finding was most pronounced in women with a BMI <24 kg/m$^2$ (239).

Several factors relate SES, low educational attainment and GDM as they might contribute to unhealthy behaviors (smoking, poor diet, physical inactivity), and an uneven distribution of access and quality of health care (220, 221, 239, 242, 243). Stressful life events, which can be directly or indirectly due to low SES, may also increase the risk for GDM (225), and low SES is a strong determinant of eating behaviors and risk for obesity (244, 245).

**Table 12** *Reference list of publications assessing the relationship between maternal socioeconomic status and gestational diabetes mellitus.*

| Reference | Country | N | SES indicator, method assessed | Association between risk factor and GDM | Prevalence of GDM |
|---|---|---|---|---|---|
| *Bo et al., 2002* | Italy | 100 impaired glucose tolerance<br>150 gestational diabetes<br>450 normoglycemia | Education levels (primary school, high school, university)<br>and current employment | Negative | University: 16.5%<br>High school: 18.6%<br>Primary school: 27.0% |
| *Janghorbani et al., 2006* | United Kingdom<br>1996-1997 | 3 933 | Neighborhood deprivation areas<br>dassified according to the Townsend index,<br>measuring material deprivation.<br>Townsend Material Deprivation Score<br>(three groups) | Neutral | 1.7% |
| *Joseph et al., 2007* | Canada<br>1988-1995 | 92 914 | Family income from tax records<br>(five groups) | Negative | Not reported |
| *Anna et al., 2008* | Australia<br>1995-2005 | 956 738 | Maternal postcode, living areas<br>(four groups) | Negative | 4.4% |
| *Bener et al., 2011* | Qatar<br>2010-2011 | 1 608 | Maternal monthly income<br>(self-reported) (five groups)<br>education, occupation (self-reported) | Negative<br><br>Neutral | 16.3% |
| *Al-Rubeaan et al., 2014* | Saudi Arabia<br>2007-2009 | 53 370 | Monthly<br>income, educational level, residency area<br>(self-reported) | Neutral | 36.6% |
| *Abouzed et al., 2015* | Australia<br>1999-2008 | 269 682 | A residential area socio-economic status (SES) score,<br>using the Australian Bureau of Statistics' Index<br>of Relative Socio-Economic Disadvantage (IRSD)<br>divided into four levels | Negative,<br>pronounced in women > 35yr | 4.4% |
| *Bouthoorn et al., 2015* | Netherlands<br>2002-2006 | 7 511 | Education level, (self-reported) (four groups) | Negative | 0.9% |
| *Collier et al., 2017* | Scotland<br>1981-2012 | 1 891 097 | An area-based measure of deprivation using<br>the Scottish Index of Multiple Deprivation (SIMD) 2012<br>(five groups) | Negative | 1.9% |
| *Song et al., 2017* | China<br>2012-2014 | 11 311 | Education level (three groups) (self-reported)<br>Household income (four groups) (self-reported) | Negative<br>Neutral | 14.6% |
| *Liu et al., 2018* | China<br>2010-2012 | 17 659 | Educational attainment<br>Family income | Negative, insignificant after adjustment<br>for BMI | 7.2 % |

*BMI*, body mass index; *GDM*, gestational diabetes mellitus

**Table 13** *Meta-analysis assessing the relationship between educational attainment and gestational diabetes mellitus.*

| Reference | Country | Inclusion criteria | Exclusion criteria | Studies | Women included | Pooled OR of maternal education level and GDM |
|---|---|---|---|---|---|---|
| *Wang et al., 2019* | China | Associations between maternal educational level and GDM<br>Primary or adjusted OR with 95% CI between the highest and lowest maternal education level provided | Review studies<br>Not in English<br>Non-human studies | 9 | 62 609 | pooled OR 0.75 (95% CI: 0.53–1.05) for women with highest education level compared with lowest education level |

*CI*, confidence interval; *GDM*, gestational diabetes mellitus; *OR*, odds ratio

### 2.2.6 MANAGEMENT AND PREVENTION

As GDM management and preventive intervention are not in the scope of this thesis, only a brief summary, according to the current care guidelines in Finland (22), will be presented.

*Self/Home monitoring of blood glucose*

The basics for management of GDM is self-monitoring of blood glucose levels. The recommendation is to measure blood glucose 5–7 times during the day, before breakfast and 1 hour after the meal, as well as before and after the main meals. Blood glucose levels should lie below the threshold values of 5.5mmol/L before breakfast and other main meals, and below 7.8mmol/L 1-h after ingestion. The main target is to find women requiring medical treatment.

*Diet*

Although the optimal GDM diet treatment has not been established, the primary aim is to meet the energy and nutrient requirements of the mother and the fetus, maintain normoglycemia, prevent excessive gestational weight gain, and reduce the need for insulin treatment, risk for macrosomia and long-term complications of GDM. The diet should be rich in high-fiber carbohydrates, polyunsaturated lipids and protein sources from vegetables and fish, chicken and low-fat meat. The recommended gestational weight gain is based on pre-pregnancy BMI, according to the institute of medicine (IOM) with the following guidelines: BMI < 18.5 kg/m$^2$: 12.5–18.0 kg; BMI 18.5–24.9 kg/m$^2$: 11.5–16.0 kg; BMI 25.0–29.9 kg/m$^2$: 7.0–11.5kg; and BMI ≥ 30.0 kg/m$^2$: 5.0–9.0 kg (246).

*Physical activity*

Research-based evidence on physical activity and its effects on GDM are sparse and studies have been done with short follow-up periods. However, physical activity is considered to reduce gestational weight gain, especially in combination with dietary therapy (247). In general, moderate physical activity is considered safe during pregnancy, in the absence of obstetric complications, and encouraged as part of a healthy lifestyle.

*Medical treatment and timing of delivery*

The main target with medical treatment is to prevent persistent hyperglycemia and associated pregnancy complications when diet treatment is insufficient. The treatment consists of insulin administration, or in milder cases, metformin administration. Insulin treatment continues until the child is born, and metformin, until one day before a planned delivery. Diet-treated women can be followed up for 7–10 days after the due date, if normoglycemic and no signs of macrosomia. In case of medication, induction of labor should be considered from 38 gestational weeks onward, latest at due date, to reduce the risks of fetal hypoxia, fetal macrosomia and shoulder dystocia.

*Prevention of GDM*

Research regarding lifestyle interventions in the prevention of GDM has been conflicting during the past decade (163). However, the heterogeneity among studies, differencies in diagnostic criteria, study settings and study populations, can, at least to some extent, contribute to the phenomenon (163). Furthermore, timing of interventions vary and interventions initiated during the latter part of pregnancy have mostly been inefficient (163).

Prior to pregnancy, optimal weight control seems to be of greatest importance in prevention of GDM, according to the current care guidelines for GDM (22). The importance of optimal pre-pregnancy health and weight control have lately been emphasized among other researchers as well (163, 248, 249). Weight loss in overweight and obese women already prior to pregnancy have been noted to, at least to some degree, reduce the risk for GDM (148, 248). In other words, physical activity prior to and during early pregnancy and a healthy pre-pregnancy diet rich in vegetables, fruits, nuts, fibers, unsaturated fats, fish and low-fat dietary products seem to have a protective effect against the development of GDM (22). A diet rich in saturated fats, cholesterol and red meat, on the other hand, seems to increase the risk for GDM (22).

During pregnancy, life-style interventions initiated as early as possible seem to reduce not only the risk for GDM, but also the risk for macrosomia (22). Hence, the purpose of life-style interventions for pregnant women is to achieve a healthier diet, to increase physical activity and to prevent excessive gestational weight gain (22). Likewise, after pregnancy, it is important to lose excessive weight and maintain the healthy life-style in order to reduce the risk for developing T2D in the future (22).

# 3 OBJECTIVES

The aim of this thesis was to evaluate the impact of four non-traditional risk factors on the risk for GDM. Further, in two of the studies included, the purpose was also to assess the combined effect of a specific risk factor and GDM on offspring birthweight.

More specifically, the study objectives for the included studies in this thesis were:

I To assess the impact of maternal height on the risk for GDM and to evaluate the combined effect of maternal height and GDM on offspring birthweight.

II To evaluate the impact of maternal body surface area at birth on later risk for GDM.

III To determine the effect of maternal smoking during pregnancy on the risk for GDM and, further, to evaluate the combined effect of smoking and GDM on offspring birthweight.

IV To explore the impact of maternal socioeconomic status, assessed as maternal income and education, on the risk for GDM.

# 4 MATERIALS AND METHODS

## 4.1 STUDY MATERIAL

### 4.1.1 VANTAA BIRTH COHORT 2009–2015

This thesis is part of a larger research project, the *Vantaa Birth Cohort study 2009–2015*, a population-based follow-up cohort initiated in 2016, with a focus to assess both short- and long-term health implications of glucose metabolism during pregnancy on the woman and her offspring. The Vantaa Birth Cohort consists of all women from the city of Vantaa, Finland, who delivered between the 1st of January 2009 and the 31st of December 2015, and their offspring. The cohort encompasses 13,530 women and 18,272 offspring. The included studies and the analyses of this thesis are based on the baseline data of the cohort study, with a primary focus to explore the impact of atypical risk factors on risk for GDM; and secondarily, in Study I and Study III, to further assess the combined effect of the specific risk factor and GDM on offspring birthweight.

### 4.1.2 STUDY POPULATION

The inclusion criteria for the four studies varies depending on the risk factor of interest (Figure 4). However, common to all included studies is that they consist only of primiparous women, in order to exclude the confounding effects of prior GDM and multiparity on risk for GDM. Additionally, they consist only of Finnish women (women born in Finland with Finnish or Swedish as native language), and women with pre-existing diabetes mellitus have been excluded from the studies.

The study populations of Study I and Study III are the same. In addition, to the abovementioned inclusion criteria, all women were aged ≥ 18 years, they delivered their firstborn singleton child between gestational weeks 37 and 42 and had complete data from OGTT. The last-mentioned criterion was used in order to have a trustworthy diagnosis of GDM. A total of 4,111 women were included.

In Study II, only women born at term after the year 1987 (when the Finnish Medical Birth Register was founded), and aged 15 to 28 years during the follow-up period, were included. A total of 1,548 women met the inclusion criteria.

In Study IV, the additional criterion for inclusion was age-related, with women aged ≥ 20 years included, mainly to ensure more reliable data of education and income. A total of 5,962 women formed the study cohort.

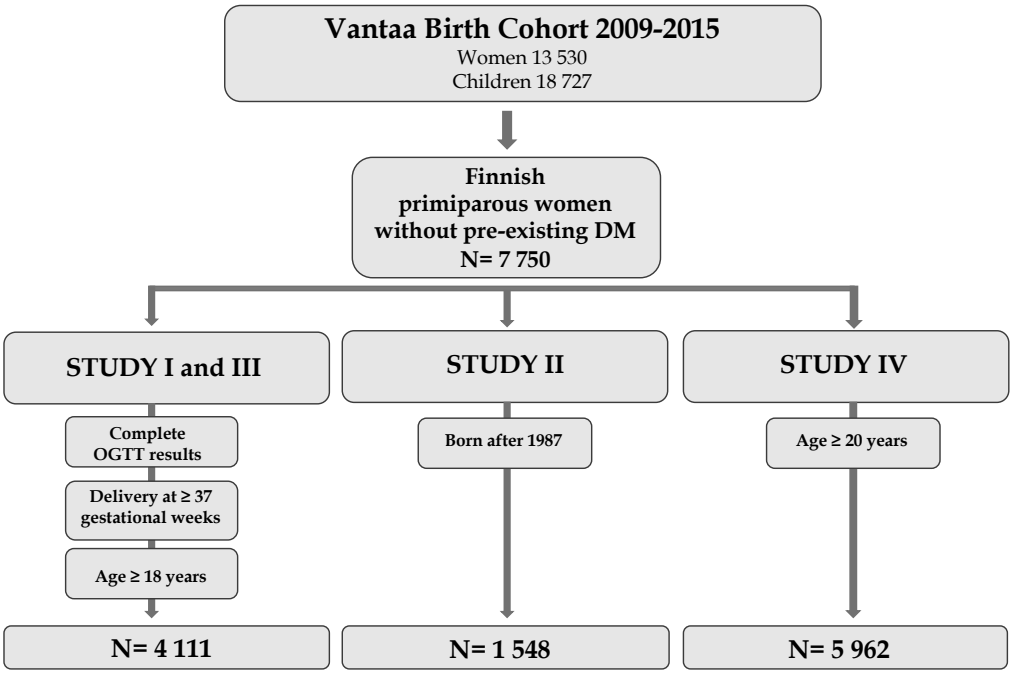



**Figure 4** Flow chart of inclusion criteria for each separate study in this thesis.

## 4.2 METHODS

### 4.2.1 DATA COLLECTION AND REGISTERS USED

***The Finnish Medical Birth Register*** was founded in 1987 and is maintained by the Finnish Institute for Health and Welfare in Finland. The register receives information on a nationwide basis about all live and stillbirths, from gestational weeks 22 or a birthweight of 500 g onward, from all Finnish maternity hospitals. From this source, data on maternal and fetal characteristics and pregnancy outcomes has been collected.

***The Finnish Social Insurance Institution***. From this source, data on medical drug reimbursements and purchases were obtained in order to exclude pre-diagnosed diabetes mellitus acquiring medication before pregnancy.
***The Finnish Tax Administration*** provided data on maternal earned and capital taxable income.
***Statistics Finland*** provided information about educational attainment according to years of schooling.
***Vantaa Health Care Patient Records***. Additional information about maternal height, pre-pregnancy weight, place of birth, native language and OGTT results were collected, as needed, from individual patient health records.

**Table 14** Data collection and registers used in Studies I–IV.

| **The Finnish Medical Birth Register** | ***Study I and III*** | ***Study II*** | ***Study IV*** |
|---|---|---|---|
| ***Mother*** | | | |
| Age at delivery | ◆ | ◆ | ◆ |
| Height | ◆ | ◆ | ◆ |
| Pre-pregnancy weight | ◆ | ◆ | ◆ |
| Parity | ◆ | ◆ | ◆ |
| Previous pregnancies* | ◆ | ◆ | ◆ |
| Use of infertility treatments | ◆ | ◆ | ◆ |
| Smoking during pregnancy | ◆ | ◆ | ◆ |
| Cohabitation status | ◆ | ◆ | ◆ |
| GDM diagnosis (ICD-10 code O24.4) | ◆ | ◆ | ◆ |
| Pathological OGTT during pregnancy | ◆ | ◆ | ◆ |
| Maternal birthweight | | | ◆ |
| Maternal birth length | | | ◆ |
| | | | |
| ***Offspring*** | | | |
| Birthweight | ◆ | | |
| Birth length | ◆ | | |
| Head circumference | ◆ | | |
| Sex | ◆ | | |
| **Statistics Finland** | | | |
| Educational attainment | ◆ | ◆ | ◆ |
| Place of birth | ◆ | ◆ | ◆ |
| Native language | ◆ | ◆ | ◆ |
| **The Finnish Tax Administration** | | | |
| Maternal annual taxable income | | ◆ | |
| **The Finnish Social Insurance Institution** | | | |
| Drug purchases | ◆ | ◆ | ◆ |
| Drug reimbursements | ◆ | ◆ | ◆ |
| Pre-existing diabetes | ◆ | ◆ | ◆ |
| **Vantaa patient healthcare records** | | | |
| OGTT laboratory results | | | ◆ |
| Supplemental information** | ◆ | ◆ | ◆ |

**miscarriages, induced abortions or ectopic pregnancies; **maternal height, pre-pregnancy weight, place of birth, native language; GDM= gestational diabetes mellitus; ICD-10= International Statistical Classification of Diseases and Related Health Problems 10th Revision; OGTT= 2-h 75-g glucose oral tolerance test*

### 4.2.2 DEFINITION OF CONCEPTS

**OFFSPRING BIRTHWEIGHT**

Offspring birthweight has been calculated as Z-scores according to sex and gestational age.

**MACROSOMIA**

Macrosomia has been defined as offspring birthweight ≥ 4500 g.

**LARGE FOR GESTATIONAL AGE**

Large for gestational age (LGA) has been defined as a birthweight > 90$^{th}$ percentile, according to gestational age at birth and sex.

**SMALL FOR GESTATIONAL AGE**

Small for gestational age (SGA) has been defined as a birthweight < 10$^{th}$ percentile, according to gestational age at birth and sex.

**PONDERAL INDEX**

Ponderal index (PI) has been calculated for estimating body proportionality at birth and has been defined as birthweight (kg) divided by birth length (m) cubed.

$PI = kg/m^3$

**BODY SURFACE AREA**

Body surface area (BSA) is an anthropometric measurement of interest that evaluates metabolic mass and body size as a whole. In our study, BSA at birth has been calculated according to the Meban BSA formula (250), which has been regarded as the most accurate formula to calculate infant BSA (251):

$BSA\ m^2 = 6.4954 \times weight\ (g)^{0.562} \times height\ (cm)^{0.320}$

Adult pre-pregnancy BSA was calculated according to the commonly used Mosteller -BSA (252) formula in adults:

$BSA\ m^2 = \sqrt{[(height\ in\ cm \times weight\ in\ kg)/3600]}$

**DIAGNOSIS OF GDM**

The screening and diagnostic criteria for GDM has remained the same during the whole follow-up period for this study in Finland. They are based on nationwide recommendations by the Finnish Current Care Guidelines since 2008 (22), and have been described in greater detail in this thesis under the section of Finnish diagnostic criteria and screening for gestational diabetes mellitus, p. 24. According to the guidelines, GDM has been defined as one or more pathological glucose values in a standard 2-h 75-g OGTT with the following diagnostic thresholds: fasting plasma glucose ≥ 5.3 mmol/L, 1-h glucose ≥ 10.0 mmol/L, and 2-h glucose ≥ 8.6 mmol/L.

### 4.2.3 CLASSIFICATION OF THE STUDY POPULATION

**HEIGHT IN STUDY I**

The women are divided into 5 groups according to height based on standardized (z-score) values containing 12.5, 25, 25, 25, and 12.5% of the total distribution. Cut-offs for height levels are I ≤ 158cm, II 159–163cm, III 164–167cm, IV 168–172cm, and V ≥173cm.

The mean height for Finnish women during the study period remained stable at 165cm (http://urn.fi/URN:ISBN:978-952-302-447-2).

**MATERNAL BODY SURFACE AREA AT BIRTH IN STUDY II**

The study population is divided into 5 levels according to birth BSA levels, based on normal distribution, and corresponding to grades containing 12.5, 25, 25, 25, and 12.5% of the total distribution. Cut-offs for birth BSA levels were: 2011cm$^2$ for level I, 2012–2170cm$^2$ for level II, 2171–2291cm$^2$ for level III, 2292–2450cm$^2$ for level IV, and ≥ 2451cm$^2$ for level V.

**SMOKING IN STUDY III**

The women are divided into three classes according to smoking status: non-smokers (I); smokers, who quit during the first trimester of pregnancy (II); smokers, who continued after the first trimester of pregnancy (III). Smoking status is self-reported.

## MATERNAL SOCIOECONOMIC STATUS IN STUDY IV

### Education

The women of the study are divided into four subgroups according to educational attainment:

*Level I*: basic education, comprising 9–10 years of school

*Level II*: upper secondary education or post-secondary non-tertiary education, comprising 11–14 years of school

*Level III*: bachelor's or equivalent education, comprising 15–16 years of school

*Level IV*: master's, doctoral or equivalent education, comprising ≥ 17 years of school.

### Income

The participants are divided into 5 income-level categories based on centiles (level I to V, and percentiles 12.5, 37.5, 62.5 and 87.5) corresponding to grades containing 12.5, 25, 25, 25 and 12.5% of the total distribution. The respective annual taxable income for the different levels were:

*Level I*: 0–11,120 €

*Level II*: > 11,120–22,855 €

*Level III*: > 22,855–29,940 €

*Level IV*: > 29,940–40,190 €

*Level V*: > 40,190 €

The mean taxable income (both earned and capital income) for each participant was calculated for the year of conception, as well as for the two preceding years. The income level was adjusted for the value of 2017 and a conversion was made based upon a consumer price index (Statistics Finland: http://www.stat.fi/til/index_en.html). In Finland, the mean annual taxable income in 2016 for women was reported to be 24,764 € (Statistics Finland: http://www.stat.fi/tup/suoluk/suoluk_tulot_en.html).

## 4.3 STATISTICAL ANALYSES

In the tables of all four studies (Study I–IV), data are presented as means with range or SD, or as counts (n) with percentages (%). According to the risk factor assessed, the study population was divided into 3–5 groups or levels, as described previously in section 4.2.3. In Studies I and III, offspring birthweight was calculated as Z-scores within the study cohort, according to sex and gestational age.

Statistical significance for the unadjusted hypothesis of linearity across categories of height (Study I), BSA at birth (Study II), income level (Study IV) and characteristics of the study participants were evaluated using the Cochrane–Armitage test for trend, linear-by-linear association test (Study IV) and analysis of variance (ANOVA) with an appropriate contrast. In Study III, statistical comparisons between the three groups according to smoking status were performed using ANOVA, and chi-square tests.

In Studies I and II, the adjusted hypothesis of linearity (orthogonal polynomial) and the association between maternal height, maternal birth BSA, and GDM prevalence were evaluated by using generalized linear models (e.g., analysis of covariance [ANCOVA] and logistic models) with appropriate distribution and link function. Models included age, education years and pre-pregnancy BMI as covariates in Study I, and age, educational attainment, pre-pregnancy BMI and smoking in Study II. By using 5-knot-restricted cubic spline regression models, a possible nonlinear relationship between offspring birthweight (Study I), maternal birth BSA (Study II) and prevalence of GDM were assessed. The length of the distribution of knots were located at $5^{th}$, $27.5^{th}$, $50^{th}$, $72.5^{th}$, and $95^{th}$ percentiles. Knot locations, also known as natural splines for restricted cubic splines, were based on Harrell's recommended percentiles or user-specified points (253).

In Study II, the relationship between maternal birth BSA and adult anthropometry (pre-pregnancy weight, height and BMI) was evaluated using correlation coefficients calculated according to the Pearson method with the following interpretations: correlation coefficients < 0.2 were considered very weak, 0.2–0.4 weak, 0.4–0.6 moderate, 0.6–0.8 strong, and > 0.8 very strong.

In Study III, adjusted differences between groups according to smoking status were evaluated using ANCOVA and logistic models. Models included age, pre-pregnancy BMI, education years and cohabiting as covariates. Hommel's multiple comparison procedure was applied to correct levels of significance for post hoc testing (at significance level 0.05).

In Study IV, the association between maternal income levels and GDM prevalence with 95% confidence intervals (CI) was assessed by using logistic regression models after adjustments for smoking, age, pre-pregnancy BMI and cohabiting status as confounding factors.

In all studies (Study I–IV), the normality of variables was evaluated graphically and by using the Shapiro–Wilk W test. Stata 15.0/15.1/16.0 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analyses.

## 4.4 ETHICAL APPROVAL

The included studies of this thesis involve no animal or human experimental studies. The study protocol has been approved by the health authority of Vantaa city, and by the ethics committee of the Hospital District of Helsinki and Uusimaa (356/13/03/03/2015, 2 November 2015), Finland. For all registers used; *the National Institute for Health and Welfare* and *Statistics Finland* have given their permission to use data for the study. According to the ethics committee of the Hospital District of Helsinki and Uusimaa and the health authority of Vantaa city, the study participants did not have to provide a Statement of Informed Consent, since all studies in this thesis are register-based and the individuals have not been contacted.

# 5 RESULTS

## 5.1 DESCPRIPTION OF THE STUDY POPULATION

The descriptive characteristics of the Finnish primiparous women from the city of Vantaa, without pre-existing diabetes mellitus and who delivered between the 1st of January 2009 and 31st of December 2015, are shown in Table 15. Mean age at delivery for these primiparas was 28.2 years (SD 5.2), and pre-pregnancy BMI 23.8 kg/m$^2$ (SD 4.5). Similarly, the descriptive characteristics of the offspring to the women are displayed in Table 16. The mean birthweight for boys was 3465g (SD 553), and for girls 3350g (SD 555). Of the boys, 2.5% were considered macrosomic (birthweight ≥ 4500g) and of the girls 1%.

**Table 15** *Descriptive characteristics of the 7,750 Finnish primiparous women without pre-existing diabetes mellitus from Vantaa city, who delivered between 1st of January 2009 and 31st of December 2015.*

| Characteristics | Women N = 7 750 |
|---|---|
| Age at delivery (years) | 28.2 (5.2) |
| Pre-pregnancy weight (kg) | 65.2 (13.6) |
| Height (cm) | 165 (6.3) |
| Pre-pregnancy BMI (kg/m$^2$) | 23.8 (4.5) |
| Body surface area (BSA) (m$^2$) | 1.72 (0.19) |
| Smoking | 1341 (17.3) |
| Years of education | 13.1 (2.8) |
| Cohabiting | 6209 (80.1) |

*BMI*, body mass index; *SD,* standard deviation
Values are means with standard deviations (SD), or counts with percentages (%)

**Table 16** *Descriptive characteristics of the offspring to the 7,750 Finnish primiparous women without pre-existing diabetes mellitus from Vantaa city, who delivered between 1st of January 2009 and 31st of December 2015.*

| Characteristics | Boys N= 3 983 | Girls N= 3 767 |
|---|---|---|
| Birthweight (g) | 3465 (553) | 3350 (555) |
| Birth length (cm) | 50.2 (2.5) | 49.4 (2.8) |
| Head circumference (cm) | 35.1 (1.7) | 34.5 (1.9) |
| Macrosomia ( ≥ 4500g) | 99 (2.5) | 37 (1.0) |
| Body surface area (BSA) (cm$^2$) | 2215 (232) | 2160 (244) |
| Ponderal index (PI) (kg/m$^3$) | 27.2 (2.5) | 27.6 (2.6) |

*SD*, standard deviation
Values are means with standard deviations (SD), or counts with percentages (%)

## 5.2 PREVALENCE OF GESTATIONAL DIABETES MELLITUS

### 5.2.1 CHARACTERISTICS OF THE WOMEN AND THEIR OFFSPRING ACCORDING TO MATERNAL HEIGHT (STUDY I)

Baseline characteristics of the 4,111 women included in Study I according to five height levels are shown in Table 17. Cut-offs for the different levels were: ≤158cm, II 159–163cm, III 164–167cm, IV 168–172cm, and V ≥173 cm. The mean height of the women was 166cm (SD 6.0) and height was positively associated with both age and educational attainment (both *p*-values < 0.001).

**Table 17** *Baseline characteristics of the 4,111 women in the cohort, according to maternal height levels.*

| Characteristics | Height levels I (≤158cm) N=442 | II (159-163cm) N=990 | III (164-167cm) N=974 | IV (168-172cm) N=1132 | V (≥173cm ) N=573 | p-value for linearity |
|---|---|---|---|---|---|---|
| Height (cm) | 156 (137-158) | 161 (159-163) | 165 (164-167) | 170 (168-172) | 176 (173-190) | |
| Age (years) | 28.7 (4.7) | 29.3 (4.8) | 29.6 (4.8) | 29.6 (4.8) | 30.1 (4.6) | < 0.001 |
| Prepregnancy BMI (kg/m$^2$) | 24.9 (4.7) | 24.6 (4.3) | 24.8 (4.6) | 24.9 (5.0) | 24.7 (5.0) | 0.93 |
| Cohabiting | 352 (80) | 802 (81) | 803 (82) | 936 (83) | 489 (85) | 0.012 |
| Years of education | 13.5 (2.5) | 13.8 (2.5) | 13.8 (2.4) | 13.9 (2.5) | 14.2 (2.5) | < 0.001 |
| Smokers[a] | 79 (18) | 158 (16) | 141 (14) | 174 (15) | 79 (14) | 0.10 |
| Fertility treatment | 34 (8) | 92 (9) | 94 (10) | 122 (11) | 60 (10) | 0.068 |

*BMI*, body mass index; *SD*, standard deviation

[a] Included those who quit smoking during pregnancy

Values are means with standard deviations or ranges (SD/range), or counts with percentages (%)

Baseline characteristics of the offspring, according to maternal height levels, are shown in Table 18. The mean birthweight was 3564g (SD 466), birth length 50.7cm (SD 2.0cm), and head circumference 35.3cm (SD 1.4) for boys. The corresponding numbers were 3458g (SD 446), 49.9cm (SD 2.0), and 34.8cm (SD 1.4) for girls. All the anthropometric measures were positively associated with maternal height, for both sexes (all *p*-values < 0.001 for linearity). Also, maternal height was positively associated with LGA offspring and inversely associated with SGA offspring (both *p*-values < 0.001 for linearity).

**Table 18** *Characteristics of the 4,111 offspring in the cohort, according to maternal height levels.*

| Characteristics | Height levels I (≤158cm) N=442 | II (159–163cm) N=990 | III (164–167cm) N=974 | IV (168–172 cm) N=1132 | V (≥173 cm) N=573 | p-value for linearity |
|---|---|---|---|---|---|---|
| Girls, n (%) | 204 (46) | 474 (48) | 447 (46) | 560 (49) | 275 (58) | 0.37 |
| Birthweight (g) | | | | | | |
| Boys | 3 435 (451) | 3 483 (443) | 3 529 (478) | 3 653 (461) | 3 700 (445) | < 0.001 |
| Girls | 3 304 (441) | 3 406 (415) | 3 466 (448) | 3 511 (465) | 3 539 (423) | < 0.001 |
| Birth length (cm) | | | | | | |
| Boys | 50.0 (2.0) | 50.3 (1.9) | 50.5 (1.9) | 51.0 (2.0) | 51.3 (1.9) | < 0.001 |
| Girls | 49.1 (2.0) | 49.7 (1.9) | 49.8 (1.9) | 50.1 (2.0) | 50.4 (1.9) | < 0.001 |
| Head circumference (cm) | | | | | | |
| Boys | 35.0 (1.5) | 35.1 (1.4) | 35.3 (1.5) | 35.5 (1.4) | 35.6 (1.4) | < 0.001 |
| Girls | 34.3 (1.5) | 34.7 (1.3) | 34.8 (1.4) | 35.0 (1.4) | 35.0 (1.3) | < 0.001 |
| Birthweight (Z-score) | | | | | | |
| Boys | -0.31 (0.94) | -0.18 (0.95) | -0.07 (1.00) | 0.19 (0.99) | 0.33 (0.99) | < 0.001 |
| Girls | -0.37 (0.94) | -0.17 (0.91) | 0.04 (1.01) | 0.15 (1.02) | 0.19 (1.01) | < 0.001 |
| LGA (>90th percentile) | 22 (5.0) | 66 (6.7) | 100 (10.3) | 148 (13.1) | 75 (13.1) | < 0.001 |
| SGA (<10th percentile) | 69 (15.6) | 122 (12.3) | 107 (11.0) | 78 (6.9) | 34 (5.9) | < 0.001 |

*LGA,* large for gestational age*; SGA,* small for gestational age*; SD*, standard deviation

Values are means with standard deviations (SD), or counts with percentages (%)

### 5.2.2 MATERNAL HEIGHT AND THE PREVALENCE OF GESTATIONAL DIABETES (STUDY I)

The overall prevalence of GDM in the study cohort was 20.7%. Figure 4 shows the relationship between GDM and maternal height at five different levels, and on a continous scale with standardized height. After adjustments for age and educational attainment, the prevalence of GDM was inversely associated with maternal height ($p$ = 0.018 for linearity) (Figure 5), and was highest in the group of shortest women (≤158cm), with a prevalence of 23.9% (95% CI: 19.9 to 27.9). The prevalence was lowest, 18.7% (95% CI: 15.5 to 21.9) in the group of avarage height women (164–167cm).

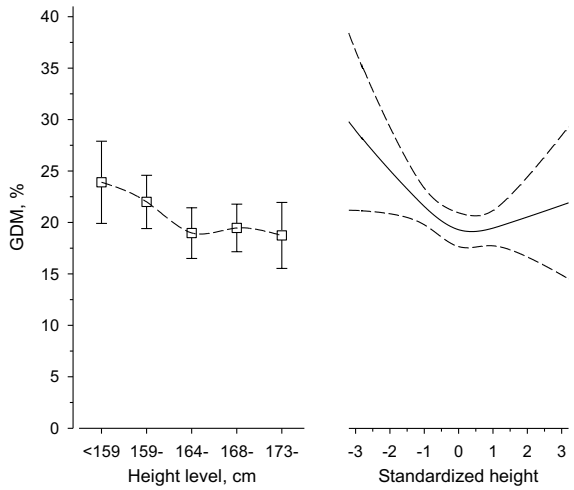



**Figure 5** Prevalence of GDM according to maternal height at five different levels, with cut-offs at I ≤ 158cm, II 159–163cm, III 164–167cm, IV 168–172cm, and V ≥173cm. The models were adjusted for age and educational attainment. Whiskers and dotted lines represent 95% confidence intervals. *GDM*, gestational diabetes mellitus. Reproduced with modifications from Masalin et al., Impact of maternal height and gestational diabetes mellitus on offspring birthweight. Diabetes Res Clin Pract. 2019;148:110-118.

### 5.2.3 CHARACTERISTICS OF THE WOMEN ACCORDING TO MATERNAL BODY SURFACE AREA AT BIRTH (STUDY II)

Tables 19 and 20 shows the birth and adult characteristics of the 1 548 women included in Study II according to their own BSA levels at birth. Cut-offs for the BSA levels were as follows: I ≤ 2011cm$^2$, II 2012–2170cm$^2$, III 2171–2291cm$^2$, IV 2292–2450cm$^2$, and V ≥ 2451cm$^2$.

Mean BSA at birth was 2231cm$^2$ (SD 472), mean birthweight 3520g (SD 472), and mean birth length 49.9cm (SD 2.0). Maternal BSA at birth was positively associated with maternal birth length and birthweight, as well as ponderal index ($p$ = 0.001 for linearity). BSA levels at birth also showed a positive association with adult pre-pregnancy weight, height, and BSA (all $p$ - values < 0.001 for linearity), as well as with pre-pregnancy BMI ($p$ = 0.004).

Assessing the correlation between maternal BSA at birth and adult anthropometry showed an overall weak correlation. The strongest relationship was found between maternal birth BSA and adult height, r = 0.31 (95% CI: 0.26 to 0.35). The correlation coefficients for pre-pregnancy weight was r= 0.16 (95% CI: 0.11 to 0.21), and for pre-pregnancy BMI r= 0.06 (95% CI: 0.01 to 0.11).

**Table 19** *Maternal birth characteristics of the 1,548 women, according to body surface area at birth.*

| | Maternal BSA- levels at birth | | | | | |
|---|---|---|---|---|---|---|
| **Maternal birth characteristics** | **I** **≤ 2011 cm²** N=183 | **II** **2012–2170 cm²** N=383 | **III** **2171–2291 cm²** N=404 | **IV** **2292–2450 cm²** N=382 | **V** **≥ 2451 cm²** N=186 | **p-value for linearity** |
| BSA ($cm^2$) | 1910 (1501-2011) | 2097 (2012-2170) | 2232 (2171-2291) | 2362 (2292-2450) | 2547 (2451-2972) | - |
| Birth length (cm) | 47.1 (1.4) | 48.8 (1.2) | 50.0 (1.1) | 51.1 (1.2) | 52.5 (1.3) | <0.001 |
| Birthweight (g) | 2755 (203) | 3185 (117) | 3508 (97) | 3836 (122) | 4321 (266) | <0.001 |
| Ponderal index ($kg/m^3$) | 26.4 (2.2) | 27.5 (2.4) | 28.1 (2.3) | 28.9 (2.2) | 30.0 (2.4) | <0.001 |

*BSA* , body surface area; *SD* , standard deviation
Values are means with standard deviations or ranges (SD/range)

**Table 20** *Maternal adult characteristics of the 1,548 women, according to body surface area at birth.*

| | Maternal BSA- levels at birth | | | | | |
|---|---|---|---|---|---|---|
| **Maternal adult characteristics** | **I** **≤ 2011 cm²** N=183 | **II** **2012–2170 cm²** N=383 | **III** **2171–2291 cm²** N=404 | **IV** **2292–2450 cm²** N=382 | **V** **≥ 2451 cm²** N=186 | **p-value for linearity** |
| Age (years) | 22.3 (2.6) | 22.3 (2.8) | 22.2 (2.6) | 22.7 (2.8) | 22.7 (2.7) | 0.024 |
| Height (cm) | 162 (6) | 164 (5) | 165 (5) | 166 (6) | 169 (6) | <0.001 |
| Pre-pregnancy weight (kg) | 60.6 (12.2) | 63.4 (14.0) | 64.2 (12.6) | 66.5 (15.0) | 68.6 (14.1) | <0.001 |
| Pre-pregnancy BMI ($kg/m^2$) | 23.0 (4.2) | 23.6 (4.9) | 23.5 (4.5) | 24.2 (5.2) | 24.1 (4.7) | 0.005 |
| BSA ($m^2$) | 1.64 (0.18) | 1.69 (0.19) | 1.71 (0.17) | 1.74 (0.21) | 1.78 (0.19) | <0.001 |
| Cohabiting | 125 (68) | 270 (71) | 285 (71) | 266 (68) | 132 (71) | 0.98 |
| Years of education | 11.3 (1.9) | 11.2 (2.1) | 11.6 (2.1) | 11.8 (2.2) | 11.9 (2.1) | <0.001 |
| Smoking[a] | 66 (36) | 127 (33) | 152 (38) | 127 (32) | 55 (30) | 0.23 |
| Fertility treatment | 3 (2) | 10 (3) | 6 (1) | 7 (2) | 4 (4) | 0.98 |

*BMI,* body mass index; *BSA,* body surface area; *SD,* standard deviation
[a] Included those who quit smoking during pregnancy
Values are means with standard deviations (SD), or counts with percentages (%)

### 5.2.4 MATERNAL BODY SURFACE AREA AT BIRTH AND LATER RISK FOR GESTATIONAL DIABETES (STUDY II)

There was an inverse, linear relationship between maternal BSA at birth and GDM prevalence ($p$ = 0.015 for linearity), after adjustments for age, educational attainment, pre-pregnancy BMI and smoking. Overall GDM prevalence in the study cohort was 12.3%. The highest prevalence of GDM, 18.1% (95% CI: 12.7 to 23.5), was seen at level I, whereas the lowest, 9.5% (95% CI: 5.7 to 13.3), at level V, as illustrated in Figure 6. The OR for GDM for those born large at level V, compared with those born small at level I was 0.43 (95% CI: 0.22 to 0.83), after adjustments for the same confounders.

Assessing the relationship on a continuous scale between maternal BSA at birth and risk for GDM showed an OR for GDM of 0.80 (95% CI: 0.68 to 0.95, $p = 0.009$) for each one SD increase in BSA at birth, after adjustments for age, educational attainment, pre-pregnancy BMI and smoking (Figure 6).
Maternal PI at birth showed no significant relationship with prevalence of GDM as the OR for GDM was 0.95 (95% CI: 0.80 to 1.12, $p = 0.53$) for each one SD increase in PI at birth, after adjustment for the same confounders.

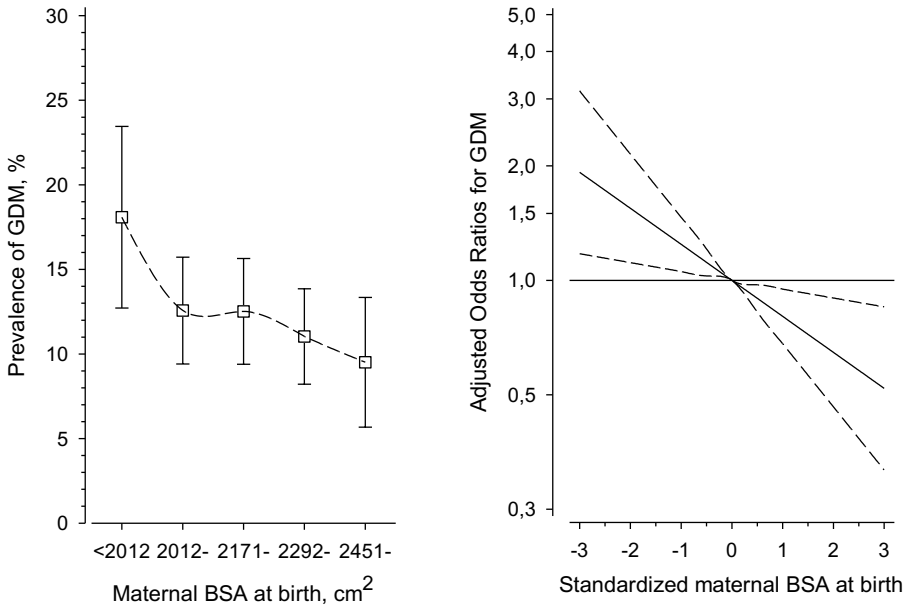



**Figure 6** The left side of the figure illustrates GDM prevalence according to maternal body surface area (BSA) at birth at five levels, with cut offs at I ≤ 2011cm$^2$, II 2012–2170cm$^2$, III 2171–2291cm$^2$, III 2292–2450cm$^2$, IV, and V ≥ 2451cm$^2$. The right side of the figure illustrates adjusted odds ratios for GDM according to maternal BSA at birth, as standardized values on a continuous scale. Reference value is the average value of BSA in the cohort (standardized Z-score value at 0). Models were adjusted for age, educational attainment, pre-pregnancy body mass index, and smoking. Whiskers and dotted lines represent 95% confidence intervals. *GDM*, gestational diabetes mellitus

### 5.2.5 CHARACTERISTICS OF THE WOMEN AND THEIR OFFSPRING ACCORDING TO SMOKING STATUS DURING PREGNANCY (STUDY III)

Characteristics of the 4,111 women in the cohort of Study III are presented in Table 21. The overall prevalence of smoking among the women in the beginning of the pregnancy was 15.5% and roughly half of them, 7.5%, quit smoking during the first trimester. Both age and educational attainment differed between the groups. Non-smokers were older, with a mean age of 30 years (SD 4.5), and had a higher educational attainment compared with smokers (both $p$ - values < 0.001 for differences between groups). Pre-pregnancy BMI was significantly lower in the group of non-smokers, but did not differ between the two groups of smokers. The distribution between hypertensive disorders among the three different smoking groups did not differ significantly.

Characteristics of the 4,111 offspring in the cohort according to maternal smoking status are shown in Table 22. Birthweight (calculated as Z-scores) differed significantly between all three groups, being highest in the group of smokers who quit smoking during the first trimester and lowest in the group of smokers who continued smoking after the first trimester ($p$ = 0.001 for differences between groups).

**Table 21** *Baseline characteristics of the 4,111 women in the cohort, according to maternal smoking status during pregnancy.*

| | Smoking status | | | |
|---|---|---|---|---|
| **Characteristics** | **I Non-smokers** | **II Smokers who quit during the first trimester** | **III Smokers who continued after the first trimester** | **p-value [a]** |
| | N = 3475 | N = 305 | N = 331 | |
| Age (years) | 30.0 (4.5) | 27.5 (4.7) | 26.5 (5.5) | <0.001 [I/II, I/III, II/III] |
| Height (cm) | 166 (6) | 166 (6) | 166 (6) | 0.30 |
| Pre-pregnancy weight (kg) | 67.8 (13.6) | 70.6 (14.8) | 72.5 (17.0) | <0.001 [I/II, I/III] |
| Pre-pregnancy BMI (kg/m$^2$) | 24.6 (4.6) | 25.7 (5.0) | 26.3 (5.6) | <0.001 [I/II, I/III] |
| Cohabiting | 2919 (84) | 235 (77) | 228 (69) | <0.001 [I/II, I/III, II/III] |
| Years of education | 14.2 (2.3) | 12.7 (2.1) | 11.2 (2.1) | <0.001 [I/II, I/III, II/III] |
| Fertility treatment | 384 (11) | 10 (3) | 8 (2) | <0.001 [I/II, I/III] |
| Hypertensive disorders[b] | 224 (6) | 27 (9) | 17 (5) | 0.15 |
| Cesarean delivery | 800 (23) | 74 (24) | 71 (22) | 0.75 |

*BMI* , body mass index; SD, standard deviation

[a] differences between groups; Hommel´s multiple comparison procedure was used to correct significance levels for post hoc testing

[b] Hospitalization due to hypertension during pregnancy

Values are means with standard deviations (SD), or counts with percentages (%)

**Table 22** *Characteristics of the 4,111 offspring in the cohort, according to maternal smoking status during pregnancy.*

| Characteristics | Smoking status<br>I<br>Non-smokers<br>N = 3475 | II<br>Smokers who quit during the first trimester<br>N = 305 | III<br>Smokers who continued after the first trimester<br>N = 331 | p-value [a] |
|---|---|---|---|---|
| Girls | 1663 (47.9) | 149 (48.9) | 148 (44.7) | 0.50 |
| Birthweight (g) | | | | |
| Boys | 3564 (460) | 3638 (467) | 3504 (519) | 0.030 [II/III] |
| Girls | 3461 (448) | 3484 (416) | 3399 (450) | 0.21 |
| Birth length (cm) | | | | |
| Boys | 50.7 (1.9) | 50.7 (2.0) | 50.3 (2.2) | 0.059 |
| Girls | 49.9 (2.0) | 49.7 (1.6) | 49.3 (2.2) | <0.001 [I/III] |
| Head circumference (cm) | | | | |
| Boys | 35.3 (1.5) | 35.3 (1.3) | 35.1 (1.5) | 0.081 |
| Girls | 34.8 (1.4) | 34.7 (1.4) | 34.7 (1.5) | 0.35 |
| Birthweight (Z-score) | 0.00 (0.99) | 0.13 (0.97) | -0.16 (1.09) | 0.001 [I/II , I/III , II/III] |
| LGA (>90th percentile) | 50 (1.4) | 6 (2.0) | 4 (1.2) | 0.70 |
| SGA (<10th percentile) | 115 (3.3) | 7 (2.3) | 19 (5.7) | 0.036 [I/III] |

*LGA,* large for gestational age; *SGA,* small for gestational age; *SD,* standard deviation

[a] for differences between groups; Hommel´s multiple comparison procedure was used to correct significance levels for post hoc testing

Values are means with standard deviations (SD), or counts with percentages (%)

### 5.2.6 PREVALENCE OF GDM ACCORDING TO SMOKING STATUS (STUDY III)

The overall GDM prevalence in the cohort was 20.7%. There was a positive association between smoking and risk for GDM. In the group of non-smokers, the prevalence of GDM was 19.8%, compared with both of the groups of smokers with a higher prevalence. In those women who quit smoking during the first trimester, the prevalence was 24.3%, whereas in the group of women who continued smoking after the first trimester, the prevalence was 26.6% ($p$ = 0.004 for differences between groups). The differences remained significant after adjustments for age, pre-pregnancy BMI, education and cohabiting ($p$ = 0.028), as shown in Figure 7.

The OR for GDM in smokers, who continued smoking after the first trimester compared with non-smokers was 1.65 (95% CI: 1.09 to 2.47), and 1.24 (95% CI: 0.90 to 1.72) for those who quit during the first trimester after adjustments for the same confounders.

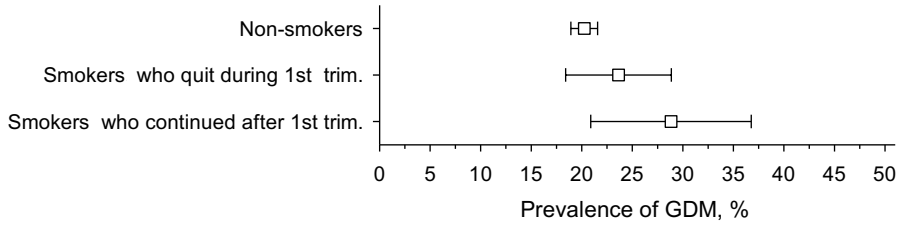



**Figure 7** Prevalence of GDM according to smoking status, with the following definitions: (I) Non-smokers, (II) smokers who quit during the first trimester, (III) smokers who continued after the first trimester. The model was adjusted for age, pre-pregnancy body mass index, education and cohabiting. Whiskers represent 95% confidence intervals.

### 5.2.7 EFFECTS OF SMOKING ON ORAL GLUCOSE TOLERANCE TEST VALUES (STUDY III)

Table 23 shows the effects of smoking status on glucose concentrations in Study III, after a standard OGTT. The effect was evident on fasting glucose concentrations ($p$ = 0.013), with a significant difference between non-smokers and smokers. Similarly, 1-h postprandial glucose concentrations ($p$ = 0.002) differed between non-smokers and smokers who continued smoking after the first trimester, but not between non-smokers and those smokers, who quit during the first trimester. However, smoking status did not affect 2-h postprandial glucose concentrations ($p$ = 0.10).

**Table 23** *Effects of smoking status on oral glucose tolerance test concentrations.*

| Glucose measurement | I Non-smokers | II Smokers who quit during the first trimester | III Smokers who continued after the first tirmester | p-value* |
|---|---|---|---|---|
| **fP glucose** | 4.77 (0.46) | 4.85 (0.47) | 4.87 (0.53) | 0.013 [I/II , I/III] |
| **1-h glucose** | 7.38 (1.74) | 7.45 (1.63) | 7.84 (1.83) | 0.002 [I/III , II/III] |
| **2-h glucose** | 6.34 (1.44) | 6.32 (1.39) | 6.25 (1.36) | 0.10 |

*SD* , standard deviation
*fP glucose* , fasting glucose; *1-h glucose* , 1-h postprandial glucose; *2-h glucose* , 2-h postprandial glucose in standard 75-g 2-h oral glucose tolerance test
* for differences between groups; Hommel´s multiple comparison procedure was used to correct significance levels for post hoc testing (p <0.05)
Values are means with standard deviations (SD)

### 5.2.8 CHARACTERISTICS OF THE WOMEN ACCORDING TO SOCIOECONOMIC STATUS (INCOME AND EDUCATION) (STUDY IV)

Table 24 shows the characteristics of the 5,692 women in the cohort of Study IV according to their annual taxable income level. The yearly taxable mean income for the women was 26,864 € (SD 14,057). There was a significant linear relationship between income level and many of the maternal characteristics. Women with the highest income level were older, taller and had a higher degree of education (all *p*-values = <0.001 for linearity). However, pre-pregnancy BMI did not differ across the income-level groups.

**Table 24** *Characteristics of the 5,692 women in the cohort according to level of income.*

| | Maternal income levels | | | | | |
|---|---|---|---|---|---|---|
| **Characteristics** | **I**<br>**0 - 11 120 €**<br>N=745 | **II**<br>**> 11 120 - 22 855 €**<br>N=1491 | **III**<br>**> 22 855 - 29 940 €**<br>N=1490 | **IV**<br>**> 29 940 - 40 190 €**<br>N=1491 | **V**<br>**> 40 190 €**<br>N=745 | **p-value for linearity** |
| Age (years) | 24.4 (4.4) | 26.6 (4.2) | 29.0 (4.1) | 31.2 (3.8) | 33.2 (3.6) | < 0.001 |
| Height (cm) | 165 (6) | 165 (6) | 166 (6) | 166 (6) | 167 (6) | < 0.001 |
| Pre-pregnancy BMI (kg/m$^2$) | 24.1 (5.4) | 24.0 (4.8) | 24.4 (4.5) | 24.1 (4.1) | 24.1 (4.1) | 0.65 |
| Pre-pregnancy obesity (BMI ≥ 30kg/m$^2$) | 101 (14) | 176 (12) | 180 (12) | 135 (9) | 68 (9) | <0.001 |
| Cohabiting | 516 (69) | 1174 (79) | 1210 (81) | 1275 (86) | 649 (87) | < 0.001 |
| Years of education | 11.7 (2.5) | 12.9 (2.3) | 13.5 (2.1) | 14.7 (2.0) | 15.7 (2.0) | <0.001 |
| Smoking[a] | 259 (35) | 326 (22) | 227 (15) | 143 (10) | 50 (7) | < 0.001 |
| Fertility treatment | 21 (3) | 70 (5) | 114 (8) | 209 (14) | 129 (17) | < 0.001 |
| Number of fetuses ≥ 2 | 5 (1) | 15 (1) | 18 (1) | 25 (2) | 20 (3) | < 0.001 |

*BMI,* body mass index; *SD,* standard deviation

[a] Included those who quit smoking during pregnancy

Values are means with standard deviations (SD), or counts with percentages (%)

### 5.2.9 PREVALENCE OF GDM ACCORDING TO INCOME LEVEL

The overall GDM prevalence in the study cohort was 20.7%. As illustrated in Figure 8 according to income levels and on a continous scale, maternal income level was linearly and inversely associated with prevalence of GDM, after adjustments for age, cohabiting, pre-pregnancy BMI and smoking ($p < 0.001$ for linearity).

The risk for GDM in the cohort increased with BMI and age. After adjustment for age, the OR for GDM was 1.90 (95% CI: 1.78 to 2.30) for each 1 SD increase in BMI. Similarly, after adjustment for BMI, the OR for GDM for each 1 SD increase in age was 1.35 (95% CI: 1.26 to 1.45).

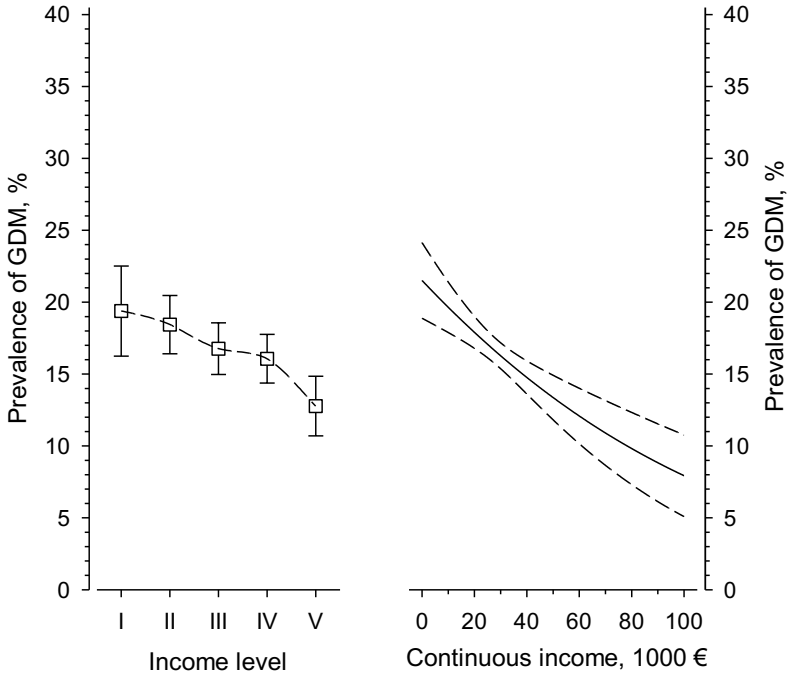



**Figure 8** Prevalence of GDM according to annual mean income level (level I–V), and on a continuous scale (1000 €). Annual income levels were classified as follows: level I, 0–11,120 €; level II, > 11,120–22,855 €; level III 22,855–29,940 €; level IV > 29,940–40,190 €; level V, > 40,190 €. Models were adjusted for age, pre-pregnancy BMI, cohabiting and smoking. Whiskers and dotted lines represent 95% confidence intervals. *GDM*, gestational diabetes mellitus, *BMI,* body mass index.
Reproduced with modifications and permission from Rönö K, et al. Impact of maternal income on the risk of gestational diabetes mellitus in primiparous women. Diabet Med. 2019;36(2):214-220. John Wiley and Sons.

Figure 9 shows the impact of educational attainment according to five maternal annual mean income levels, adjusted for smoking, age, pre-pregnancy BMI, cohabiting and smoking. GDM prevalence was inversely associated with both income ($p$ = 0.007) and education (0.039), and there was no significant interaction between these two factors.

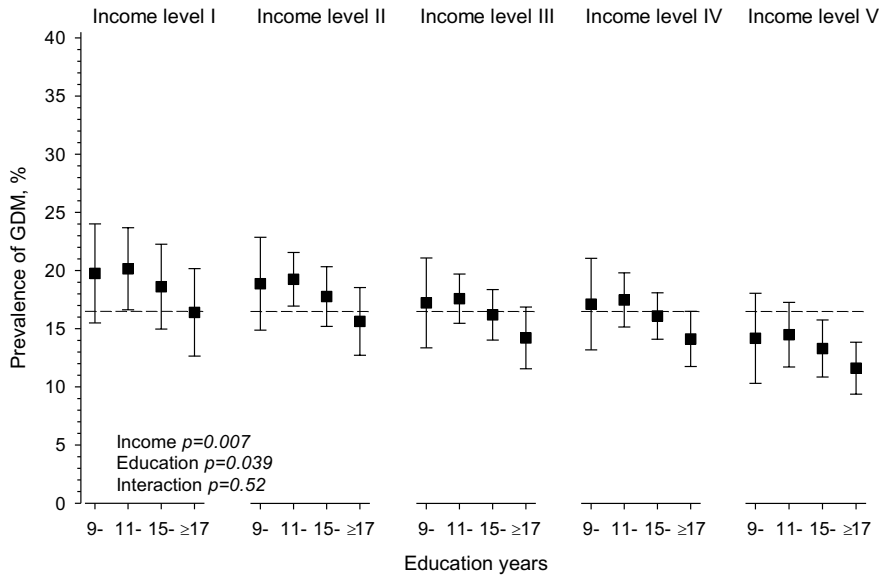



**Figure 9** The relationship between GDM prevalence and educational attainment according to five maternal annual taxable mean income levels, adjusted for age, pre-pregnancy BMI, cohabiting and smoking. The following definitions were applied for educational attainment: 9–10 years, basic education; 11–14 years, upper secondary education or post-secondary non-tertiary education; 15–16 years, bachelor´s or equivalent education; and ≥ 17 years, master´s, doctoral or equivalent education. Similarly, for income levels: level I, 0–11,120 €, level II, > 11,120–22,855 €; level III > 22,855–29,940 €; level IV, > 29,940–40,190 €; and level V, > 40,190 €. Whiskers show 95% confidence intervals, and the dotted line is the mean GDM prevalence in the study cohort. *GDM*, gestational diabetes mellitus; *BMI*, body mass index

## 5.3 IMPACT OF A NON-TRADITIONAL RISK FACTOR AND GESTATIONAL DIABETES ON OFFSPRING BIRTHWEIGHT

### 5.3.1 MATERNAL HEIGHT, GESTATIONAL DIABETES AND OFFSPRING BIRTHWEIGHT (STUDY I)

Figure 10 illustrates the combined effect of maternal height, GDM and their interaction on offspring birthweight, adjusted for age, pre-pregnancy BMI and educational attainment. In women without GDM, maternal height was positively associated with offspring birthweight ($p < 0.001$ for trend) across the five height levels. However, maternal height had no impact on offspring PI.

In women with GDM, maternal height was similarly associated with offspring birthweight ($p < 0.001$ for trend), with the exception of women with average height (159–167cm), in whom GDM had no significant impact on offspring birthweight. The combined effect of maternal stature and GDM was similar for boys and girls.

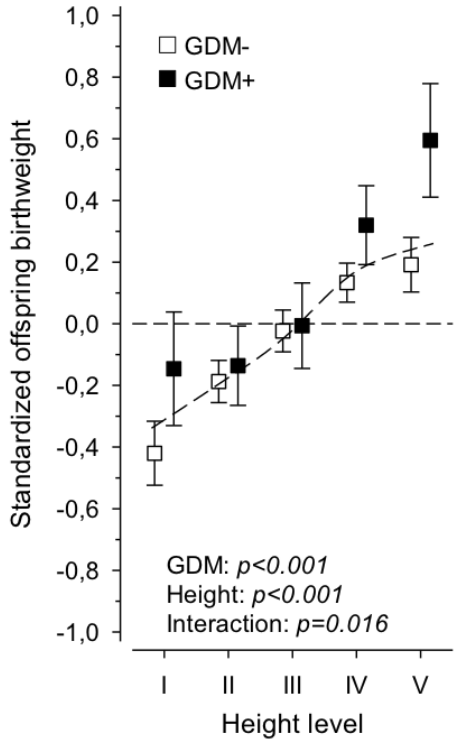



**Figure 10** Impact of maternal height, GDM and their interaction on offspring birthweight, according to height at five levels with cut-offs at I ≤ 158cm, II 159–163cm, III 164–167cm, IV 168–172cm, and V ≥173cm. The model was adjusted for age, pre-pregnancy body mass index, and education. Offspring birthweight has been calculated as Z-scores, according to gestational age and sex. Whiskers represent 95% confidence intervals. *GDM*, gestational diabetes mellitus. Reproduced with modifications from Masalin et al., Impact of maternal height and gestational diabetes mellitus on offspring birthweight. Diabetes Res Clin Pract. 2019;148:110-118.

### 5.3.2 SMOKING DURING PREGNANCY, GESTATIONAL DIABETES AND OFFSPRING BIRTHWEIGHT (STUDY III)

The impact of maternal smoking during pregnancy, GDM and their combined effect on offspring birthweight is shown in Figure 11. After adjustments for maternal age, educational attainment and pre-pregnancy BMI, the effect of smoking on offspring birthweight was significant ($p$ = 0.010), whereas the effect of GDM was not. Additionally, the interaction between GDM and smoking was significant. In the absence of GDM, offspring birthweight was lowest in the group of women who continued smoking after the first trimester. If the pregnancy was complicated by GDM, offspring birthweight did not differ significantly across the smoking groups, not even in the group of women who continued smoking after the first trimester.

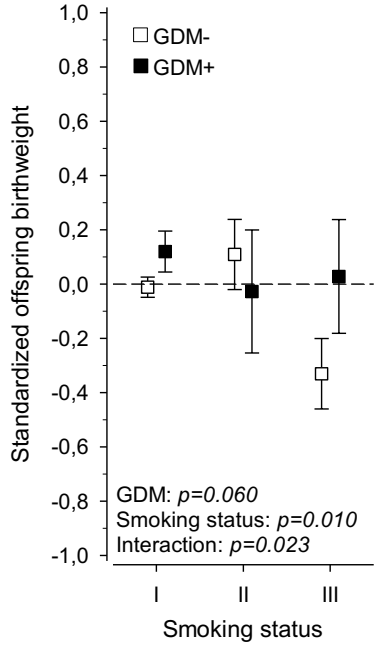



**Figure 11** The effects of smoking status, gestational diabetes and their interaction on offspring birthweight, calculated as Z-score according to sex and gestational age. The three smoking groups were defined as follows: (I) non-smokers, (II) smokers who quit during the first trimester, and (III) smokers who continued after the first trimester. The model was adjusted for age, pre-pregnancy body mass index, education and cohabiting, and whiskers represent 95% confidence intervals. *GDM*, gestational diabetes mellitus.
Reproduced with modifications and permission from Masalin et al., Impact of smoking on gestational diabetes mellitus and offspring birthweight in primiparous women. Acta Obstet Gynecol Scand. 2020 Dec;99(12):1632-1639. John Wiley & Sons.

## 5.4 SUMMARY OF GDM PREVALENCE IN THE FOUR STUDY COHORTS (STUDY I–IV)

To summarize, Table 25 shows the prevalence of GDM in the four study cohorts (Studies I–IV) according to risk factors assessed. It should be noted that the same cohort was utilized in Studies I and III.

**Table 25** *Unadjusted prevalence of GDM in the four studies of the Finnish primiparous women without previously diagnosed diabetes mellitus from Vantaa city, according to risk factor assessed.*

| | Study I<br>**Height**<br>N=4 111 | Study II<br>**Body surface area**<br>N=1 548 | Study III<br>**Smoking**<br>N=4 111 | Study IV<br>**Socioeconomic status**<br>N=5962 |
|---|---|---|---|---|
| **Additional inclusion criteria** | Complete OGTT<br>Age ≥ 18 years<br>Delivery ≥ 37 gestational weeks | Born after 1987 | Complete OGTT<br>Age ≥ 18 years<br>Delivery ≥ 37 gestational weeks | Age ≥ 20 years |
| **GDM prevalence (%)** | **20.7** | **12.3** | **20.7** | **16.5** |

*GDM*, gestational diabetes mellitus; *OGTT*, oral glucose tolerance test

# 6 DISCUSSION

## 6.1 MAIN FINDINGS

### 6.1.1 PREVALENCE OF GDM

The overall prevalence of GDM in Studies I-IV encompassing Finnish primiparous women varied largely, and ranged from 12.3% in Study II to 20.7% in Studies I and III. In Study IV, the prevalence was 16.5%. During the same timespan, from 2009 to 2015 the nationwide prevalence of GDM in Finland increased from 9% to 16% (7). Noteworthy however, is that the nationwide estimation included both primi- and multiparous women. Parity is considered to independently increase the risk for GDM (171), which has been shown especially in younger women (254).

The large variations in prevalence numbers across the different studies reflects the heterogenity of the study cohorts and emphasizes the importance of taking into account the characteristics of the background population and the prevalence of women at high risk for GDM when comparing prevalence numbers between studies.

Since Study I and III shared the same study cohort, their prevalence numbers were the same. The cohort differed from the other ones as it only included primiparous women, with complete results from OGTTs. Thus, this population can be considered at a higher risk for GDM, since screening of GDM in Finland is performed in all primiparous pregnant women, with the exception of those at low risk (women aged < 25 years, with a BMI 18.5–25kg/m$^2$, and with no family history of T2D) (22).

Similarly, the lower prevalence of GDM in Study II can probably be explained by a study cohort consisting of rather young women at a lower risk for GDM. The mean age of the primiparous women was 22 years, due to the restriction of women born only after 1987, when the Finnish Medical Birth Register was founded. The mean age of primiparas in Finland between 2010 and 2015 increased from 28.2 to 28.5 years (7).

In Study IV, the only additional inclusion criteria, as compared with the other studies, was that it included only primiparous women aged ≥ 20 years. However, although the prevalence rate can be considered quite high, it mimics the prevalence rate on a nationwide level. The high prevalence in this study,

as well as in Finland in general, is probably largely explained by a wider recognition of risk factors and the comprehensive national GDM screening strategy, as well as by the early-pregnancy screening of women considered to be at highest risk (22, 94). Further, the prevalence of well-acknowledged risk factors for GDM such as advanced maternal age at delivery, as well as obesity have been increasing in parallel among pregnant women in the country (7).

### 6.1.2 IMPACT OF NON-TRADITIONAL RISK FACTORS ON GDM

*Maternal height*

According to the findings of Study I, maternal height was inversely associated with the risk for GDM. The prevalence was highest, 24%, in the group of shortest women (≤ 158cm), and lowest, 19%, in the group of women of average height (164-167cm).

Adult short height increases risk for glucose intolerance, hypertension and cardiovascular diseases (192, 255, 256). Our findings are in line with earlier reports regarding the relationship between stature and GDM. Some older studies have indicated maternal stature not to differ between women diagnosed with GDM compared with those without GDM (191). However, the majority of studies have shown an inverse relationship between stature and GDM, either by comparing stature in women with GDM to those without (187, 188, 202), or by assessing the prevalence of GDM according to maternal height classes (189, 257-259). A meta-analysis from 2019 reported the risk for GDM to decrease for every additional 5-cm in height (23). Our findings, showing the effect of maternal stature on GDM risk to be pronounced explicitly in women of shorter than average height, endorse these earlier findings, as well as the findings of a previous study from the Vantaa Birth Cohort (190). Mean height of the women in our study cohort was 166cm, which corresponds to the mean height of Finnish women (165cm) during the study period (http://urn.fi/URN:ISBN:978-952-302-447-2 ).

Our findings also support the hypothesis of a link between a short stature and a reduced abilty to produce insulin (9), predisposing shorter individuals to sub-optimal glucose regulation. This might be due to a sub-optimal prenatal growth that has affected adult stature and metabolic health (193, 194, 260) impaired β-cell function (192), or through alleles for short stature being linked with risk for GDM, as has been found between short stature and risk for T2D (197). Moreover, low socioeconomic status has been inversely associated with stature (196), as seen in Study IV as well, in which a lower income level was negatively associated with stature (261). Similarly, in our cohort, women of

shorter height were less educated and were more likely to be smokers compared with taller women. In Study III, we showed smoking during pregnancy to increase the risk for GDM (262), and in Study IV education seemed to be inversely associated with GDM (261). However, the idea of obesity as a possible mediator between short stature, lower educational attainment and GDM was not emphasized in our cohort, as pre-pregnancy BMI did not differ between the different height classes.

A short adult height similarly increases the risk for T2D (181, 192). Studies both in pregnant (190) and non-pregnant populations (182) have shown that postprandial values in a standard OGTT are higher in short people, with no difference in fasting values. Since muscle tissue is the major tissue for metabolizing glucose in the body (183), this still raises the question of whether the diagnosis of GDM with the same fixed glucose dose in all pregnant women, regardless of maternal height, possibly leads to over-diagnosis of GDM in short people. In other words, would the diagnosis be more reliable if the height of the woman was accounted for when planning for the amount of glucose given in an OGTT?

### *Maternal low birthweight*

In Study II, we found BSA at birth to be positively associated with adult anthropometry and to be linearly and inversely associated with risk for GDM. Only a few previous studies have assessed the relationship between maternal body size at birth as a whole and GDM. In 2017, a Danish study showed PI to be negatively associated with GDM (211). However, the sample size was rather small. In contrast, we did not detect any significant relationship between maternal PI and risk for later GDM.

However, maternal low birthweight has in many studies been reported to increase the risk for GDM (202, 204, 205, 263), supporting the DOHaD hypothesis and underscoring the importance of early nutritional state in the prediction of adult health (18). Additionally, a U-shaped relationship between birthweight and GDM has in some studies been detected (207, 208, 210).

The conflicting results can be explained by differences in study settings, with some studies lacking a large enough comparison group for macrosomic infants (204, 263), as well as by differences in ethnicity (264). Further, offspring born to GDM mothers are prone to be macrosomic (11, 13, 71) and offspring born LGA (13, 265), as well as maternal GDM itself (265), increases the risk for offspring metabolic disorders later in life (13, 16). Still, the effect of maternal

obesity as a potential mediator should be recognized, since maternal obesity, independently, is known to increase the risk for macrosomia (265).

However, compared with birthweight, birth length is thought to predict adult stature even better (260), and stature is associated with the susceptibility to many non-communicable diseases, such as cardiovascular and respiratory diseases (180). In Study I, we showed an inverse relationship between stature and GDM and proposed stature to be of importance in glucose metabolism. Hence, we also wanted to estimate the maternal size at birth as a whole, taking both birthweight and birth length into account, when assessing the risk for GDM.

BSA is used in studies for estimations of body size and body composition since it is an absolute measure defined by the whole body surface area. In pediatrics, infants´ BSA is important for drug metabolism, total body water composition, and thermoregulation (251). The effect of body size as a whole, and later risk for GDM, has been sparsely evaluated previously. Possibly, taking the whole metabolic mass of a newborn into account, using BSA as an indicator, a more accurate and realistic estimation of the risk for GDM could be obtained. Our results endorse the theory of DOHaD and underscores the importance of early nutritional and metabolic state in life that can have long-spanning effects on organ development, organ function and adult morbidity (19, 142). More specifically, findings support the idea that low birthweight could cause an impaired glucose tolerance in adulthood, possibly due to impaired endocrine pancreas development and β- cell function (199).

### *Maternal smoking during pregnancy*

In Study III, we found smoking to be positively associated with risk for GDM, especially in the group of smokers who continued smoking after the first trimester. Similarly, both fasting and 1-hour glucose concentrations were significantly higher in smokers who continued smoking after the first trimester compared with non-smokers. 2-hour glucose concentrations, however, did not differ according to smoking status.

The overall prevalence of smokers in the cohort was 15.5%, of which roughly half of the women continued smoking after the first trimester. The findings are in line with the nationwide prevalence of smoking during pregnancy in Finland, estimated between the years of 1991–2015 (266).

The relationship between smoking and the risk for T2D seems to be positive in many studies (217, 218). In line with this, the WHO has newly endorsed smoking as a modifiable risk factor for T2D (216). However, the relationship

between smoking and GDM remains controversial, with some studies reporting a positive (219-222), a few studies a negative (26, 223), and two meta-analyses (24, 25) and a recent cohort study a neutral relationship (229).

Understanding the differences in study settings is important. Mostly, smoking status of the pregnant woman has been self-reported or assessed in different manners depending on the study setting. Further, self-reported information among pregnant women is probably underestimated, as reported in studies that have validated given information using biochemical markers, such as cotinine (267). Diagnostic criteria for GDM have also evolved over time and still vary greatly between countries. Moreover, analyses have been performed controlling for different variables and the confounding effect of socioeconomic factors or weight gain following smoking cessation in early pregnancy (268), for example, should be recognized. Socioeconomic deprivation (26, 27), which smoking can be linked to (26, 269), as well as excessive weight gain during pregnancy (270), are potential risk factors for GDM. Interestingly, D-vitamin levels also seem to be lower in pregnant smokers (271), and D-vitamin deficiency possibly increases the risk for GDM (272).

Few studies have assessed the effects of smoking on glucose concentrations after an OGTT in pregnant women. However, in two previous studies (228, 229), and in studies among non-pregnant smokers (231, 273), 1-h postprandial levels have been reported to be elevated. In Study III, we found both fasting and 1-h glucose concentrations to be higher in women that continued smoking after the first trimester, compared with non-smokers. In those who quit during the first trimester, the 1-h glucose concentration did not differ compared with non-smokers, although the fasting glucose concentration remained higher. This could indicate that the acute effects of smoking are already reversible during pregnancy since OGTT is mostly, except in women at high- risk, performed during the latter part of pregnancy. In line with this idea, a previous study among non-pregnant smokers showed that insulin sensitivity improved, but not to normal levels, after 1–2 weeks of smoking cessation (274). Previously, little impact of smoking on fasting glucose values has been reported (228, 230, 231, 273). However, similar to our findings, a recent cohort study from Greece reported fasting glucose concentrations to be higher in pregnant smokers (229). HbA1c values have, nevertheless, in some previous studies among pregnant women been higher in smokers, compared with non-smokers (219, 228, 229), highlighting the chronic effects of smoking on glucose homeostasis.

Chronic smoking is recognized to increase IR by affecting β-cell function and insulin secretion, as well as by increasing fasting glucagon levels (218, 226).

The mechanism behind the acute effects on smoking on glucose metabolism remains unclear. Hypotheses of higher 1-hour postprandial concentrations and lower 2-hour postprandial concetrations due to increased glucose absorption and accelerated gastric emptying have been reported (228, 230). Although, the opposite has also been proposed (226), that a decreased gastric emptying in smokers could explain the lower postprandial levels reported in other studies. However, in contrast to those findings, we found no differences in 2- hour postprandial levels. Still, one can only speculate how the growing uterus in pregnant women affect gastric emptying and glucose absorption.

### *Maternal socioeconomic status*

In Study IV, we evaluated the effect of maternal SES, assessed as maternal annual mean taxable income and educational attainment, on risk for GDM in primiparous women. The relationship between both of these indicators and GDM was inverse and showed no interactions.

The relationship between SES and risk for GDM has in previous studies been assessed using different indicators for SES. Mostly, an inverse relationship between the area of residence and GDM has been reported (26, 27, 275), although neutral relationships have been identified as well (29, 30). Similar to our results, educational attainment has mostly been inversely associated with GDM (28, 239, 276), although neutral (29, 238) relationships have also been reported, including in a meta-analysis from 2019 (240). However, a subgroup analysis revealed an inverse relationship, after adjustments for BMI (240). The inverse relationship has been thought to be, at least partly, mediated by overweight and obesity (28, 240).

Using different indicators for SES when assessing the effects on various health outcomes makes comparisons between studies difficult since different indicators might symbolize different health-related behaviors. As an example, educational attainment has been acknowledged to reflect a person's knowledge-related assets (232). Moreover, education might also be a predictor of income and wealth which can have a direct impact on material resources, area of residence, health-promoting factors such as healthy diet or exercise, and accessibility to different health services (232). However, the causal effect of income or education on health is still not clear and also a reverse causation is possible. People with poor health might have disadvantages when it comes to education and earning (277). Additionally, area of residence is a crude measure of SES (232), and the true SES of the inhabitants of any given region can vary greatly between individuals.

In Study IV, we had the unique opportunity to assess maternal mean taxable income levels obtained from the Finnish Tax Administration, on risk for GDM. Similar to our findings, one previous Canadian study evaluated the effects of objectively collected family income received from tax records (237) on GDM, and showed a negative relationship. The same relationship was detected in a study from Qatar, assessing self-reported maternal monthly income and GDM (238). However, a recent study from China in 2017 (239) detected no relationship between self-reported household income and GDM, neither did an older study from Saudi Arabia in 2014 (29), when assessing self-reported maternal monthly income and risk for GDM. Using income as an indicator differs between studies, propably depending on information available, but also depending on cultural differences. It is, however, important to recognize the differences.

When assessing maternal SES using income as an indicator, differences between study setting occur. Income is a parameter that changes over time depending on employment and salary status. Additionally, assets transfer when starting a family, hence, partners´ SES is also likely to play a role (232). Household income estimates the disposable income for individuals within the same household, assuming an even distribution of income, which is not always true (232). However, in countries where the employment rate of women is low, household income is probably the most accurate parameter to use. In Finland, on the other hand, where the employment rate of women is 71.8%, and thus, near the employment rate of men at 73.3% (278), one can consider maternal income to represent her health behavior more on an individual level.

Our findings support a negative relationship between a low socioeconomic position and GDM. A low SES has been linked to unhealthy eating behaviors and obesity (244, 245), smoking (26, 269) and short stature (23, 196), all of these having a negative influence on GDM. Since educational attainment is likely to influence disease awareness and health-related choices, women with higher educational attainment could be expected to have a reduced risk for GDM. Similarly, a higher income is likely to enable better access to healthcare and a more affordable consumption of a health-promoting lifestyle in general (diet, physical activity). Lastly, the positive effects on health for individuals with a higher SES are also thought to some extent be mediated by social networks that better protect against loneliness and thus promote better health outcomes (279).

### 6.1.3 THE COMBINED EFFECT OF A NON-TRADITIONAL RISK FACTOR AND GDM ON OFFSPRING BIRTHWEIGHT

*Maternal height and GDM*

In Study I, we evaluated the simultaneous effect of maternal height and GDM on offspring birthweight, as both GDM (11, 71) and stature (280-283) are known to affect offspring size at birth. In our cohort of primiparous women, in the absence of GDM, we found maternal height to be positively associated with offspring birthweight. Similarly, maternal height was positively associated with LGA infants. However, if the pregnancy was complicated by GDM, offspring birthweight was increased, as compared with women with no GDM, but only in the extreme height categories. In the group of average height women, GDM had no impact on offspring birthweight.

The positive relationship between maternal height and offspring birthweight was expected, as reported in the literature (280, 281). However, one previous study has reported the relationship to be dependent on ethnicity, so that the effect would be significant in white, black and Asian women, but not in Hispanic women (283). Additionally, the positive relationship between height and LGA infants, as well as the negative relationship between height and SGA infants has recently been detected in a German study (284). That we found no relationship between maternal height and offspring PI could suggest that the body proportionalities would not be affected by maternal stature to a significant extent.

Maternal stature reflects both genetic factors, as well as environmental and nutritional conditions during the childhood and adolescence of the mother (281, 285). The relationship between stature and offspring birthweight, in turn, is thought to mainly reflect a hereditary component (281). However, the effect of socioeconomic disadvantage (196, 286-288), as well as early malnutrition (180, 289) is similarly difficult to rule out, since both of them can affect fetal growth negatively. Moreover, physical constraint due to a narrow pelvis might limit fetal growth (290).

Interestingly, when evaluating the simultaneous effect of GDM and maternal height on offspring birthweight, we found a significant interaction. When the pregnancy was complicated by GDM, offspring birthweight was increased, but only in the extreme height categories. According to Pedersen's hypothesis, glucose is the main substrate for fetal growth and elevated maternal glucose concentrations might lead to exaggerated fetal growth (11). Given that the GDM diagnosis in Finland is based on a standard OGTT, with a fixed amount

of 75-g oral glucose administration independent of height (22), one can hypothesize that tall women, with proportionally more metabolically active muscle tissue, diagnosed with GDM, might have a more severe degree of glucose impairment, compared with GDM women of shorter stature. Thus, the impact of GDM on offspring birthweight could be more pronounced in tall women, leading more often to LGA infants. On the other hand, in short women with a limited amount of muscle mass, even a mild elevation of blood glucose could be more likely to affect fetal growth.

In women of average height, the impact of GDM on offspring birthweight seems to be less. This could probably be explained by a milder GDM in women in whom the impact of height on glucose regulation would be less significant. The idea gets supported by the finding in a recent cohort study from Australia, in which women with diet-treated, and hence mild, GDM showed no increased risk for macrosomia compared with non-diabetic controls (291).

### *Maternal smoking during pregnancy and GDM*

The prevalence of smoking during pregnancy has been declining over the last decades (267), however, smoking is still of a major concern with several adverse pregnancy complications, such as an increased risk for pre-term birth, perinatal mortality and stillbirth (267). Moreover, of exogenous environmental factors affecting fetal growth, studies indicate rather uniformly that smoking is inversely associated with offspring birthweight (267, 292).

The effect of smoking on offspring birthweight in Study III was in line with findings from the literature. In the absence of GDM, offspring birthweight was lowest in primiparous women who continued smoking after the first trimester. However, we found a significant interaction between GDM and smoking status. In women with GDM, offspring birthweight was not reduced, not even in those women who continued smoking after the first trimester.

The mechanisms behind the relationship are not fully understood. Nicotine and carbon monoxide most likely play an important role, impairing fetal oxygenation and nutrition transfer due to a reduction in uteroplacental circulation, as well as by binding to fetal hemoglobin (267, 292). Interestingly, there is also evidence of a possible link between some specific maternal metabolic genes and smoking with respect to fetal growth (267). However, the adverse effects of smoking during pregnancy on fetal growth are likely to be reversible (293), as well as dose-dependent (292), at least to some extent. In line with this idea, in Study III, in those women who quit smoking during the first trimester offspring birthweight was not lower, but rather was higher

compared with non-smokers. However, the effect of eventual gestational weight gain as a consequence of smoking cessation in early pregnancy (268) that could increase offspring birthweight (294, 295) should also be acknowledged as a possible explanation behind this observation.

Few studies have evaluated the combined effect of smoking and GDM on offspring birthweight. In 2000, a Swedish study assessed this relationship in 499 women (219). Opposite to our findings, they found offspring birthweight to also be lower in heavily smoking women with elevated glucose levels and concluded that the growth-restricting effects of smoking suppresses any expected growth stimulation from elevated glucose concentrations (219). Nevertheless, the women were thinner and shorter, which could serve as possible confounding factors, as maternal anthropometry is known to affect newborn body size (280). In Study III, women who smoked had a higher pre-pregnancy BMI. However, they also had a lower degree of educational attainment, which in turn, is inversely associated with BMI (296) and, thus, could serve as a plausible explanation for the differences.

## 6.2 STRENGTHS OF THE STUDY

The included studies (Studies I–IV) in this thesis have several strengths. They basically share the same study cohort, with some differences in the inclusion criteria depending on the study setting for different risk factor assessed. The study cohort is comprehensive and homogenous since it includes all Finnish primiparous women from the city of Vantaa (the fourth biggest city in Finland with 220,000 inhabitants) who gave birth during a 7-year follow-up period (2009–2015) and had no pre-existing diabetes mellitus. Only primiparas were included in order to exclude the confounding effects of previous GDM or multiparity on risk for GDM.

Based on the Finnish Current Care Guidelines published for the first time in 2008 and with an updated version in 2013, the diagnostic criteria for GDM in a standardized 2-h 75-g OGTT remained the same during the whole study period.

In Finland, all individuals have a personal identification number, which facilitates the combination of data from several national registers, administrated by Finnish authorities, on a personal level. Hence, data on educational attainment, pre-existing diabetes mellitus, drug purchases and drug reimbursements used in Studies I–IV are objectively collected as received by Statistics Finland and the Finnish Social Insurance Institution. Likewise, data on maternal annual taxable income used in Study IV is not self-reported,

rather received from the Finnish Tax Administration. Additionally, missing data on maternal anthropometric values and OGTT results have been completed by manually going through individual patient health records from the city of Vantaa.

Finally, the reliability and quality of the Finnish Medical Birth register, which forms the basis of study data in all four studies (Studies I–IV), can be considered good (297). Additionally, the attendence rate in public antenatal care among pregnant women in Finland is impressively high, with almost all women using the service (32).

## 6.3 LIMITATIONS OF THE STUDY

Since the study materials and methodology of the four studies (Studies I–IV) are based on an observational register-based cohort, we lacked information on some well-acknowledged risk factors for GDM such as family history of diabetes and gestational weight gain. Further, we had no data on lifestyle-related factors including diet or physical activity of the women.

In Study I, we cannot ensure that the information on maternal height, even though objectively collected from the Finnish Medical Birth Register and Vantaa Health Care patient records, was objectively measured for all women, rather information on height might also have been self-reported. We also lacked information on body composition and birthweight of the mothers. Likewise, paternal anthropometric data were not available. Additionally, although all participants included had complete OGTT results, we had no other information on metabolic parameters, IR or glycemic control during pregnancy. Hence, the relationship between those and offspring birthweight remain unknown.

In Study II, it is important to acknowledge that the Finnish Medical Birth Register, from which we received the obstetrical and perinatal data utilized in this study, started to collect data on a nationwide basis only in 1987. Hence, as the cohort consisted of young primiparas with a mean age of 22 years, implementations of the results on older pregnant women is restricted.

In Study III, information regarding smoking status was self-reported and smoking status prior to pregnancy was unknown. Additionally, we lacked objectively measured data, such as biochemical cotinine markers or carbon monoxide expiration detectors, for validation of smoking history. Moreover, the amount of cigarettes smoked/day was missing.

In Study IV, data on paternal indicators for assessing SES, such as annual taxable income, was not available.

In all four studies (Study I–IV) we included only Finnish women, with either Finnish or Swedish as their native tongue. Thus, our results cannot necessarily be generalized to apply to different ethnic populations.

## 6.4 CLINICAL IMPLICATIONS AND PUBLIC HEALTH PERSPECTIVES

GDM prevalence is globally increasing (3, 4). Taking into account the adverse short- and longterm effects on both the woman and her offspring, the importance of identifying women at risk is highlighted – not just for prevention of GDM, but also for prevention of other metabolic disorders from a lifespan perspective. Also, ceasing the vicious cycle and transgenerational transmission of GDM is essential in order to improve the metabolic health of future generations.

It has been reported that over 50% of pregnant women diagnosed with GDM have one or more risk factors (9). However, GDM is a heterogenic disorder (132), and 40% of GDM cases are unidentified when using a risk factor–based screening stategy (77, 78). As the most commonly used risk factors (e.g., increased BMI, advanced age, a family history of diabetes) can be considered traditional ones, identifying non-traditional ones is also important.

In Finland, the public health care system offers antenatal healthcare for all pregnant women. The aim is to support a healthy pregnancy by offering health guidance to all pregnant women, to reduce inequalities between socioeconomic groups, and to find those at high risk for pregnancy complications (32). The attendance rate is impressively high, with only 0.2–0.3% of the pregnant women not using the service (32). Hence, the system offers an excellent opportunity for finding pregnant women at risk for factors that could adversely influence their pregnancy. However, increasing evidence shows that the pre-conceptional health of a woman is also of great importance when it comes to offspring health (298), and that screening of risk factors should already be initiated before, rather than during, pregnancy (298). Thus, the mission to identify women at risk should be established already in school and student healthcare, latest in antenatal care, and at fertility and maternity clinics when pregnant. Similarly, acknowledgment of risk factors for GDM could be introduced in the curriculum of reproductive education.

The results of this thesis suggest additional risk factors that could be taken into account when assessing a woman's risk for GDM. These factors are not likely to predict the risk for monogenic or autoimmune GDM, but seem to play a role in β-cell function and development of IR. The risk factors are to some extent connected, which emphasizes the importance of assessing the women and her risk as a whole.

***Height.*** Adult height reflects genetic, nutritional and socioeconomic circumstances during childhood and is associated with later health and maternal–fetal outcomes (180). Short maternal stature should be acknowledged for increasing the risk for GDM. Special attention should also be paid to short and tall women diagnosed with GDM, since they seem to be at greater risk for delivering larger offspring. However, exact height limits for risk estimations are difficult to define, since mean height varies across countries (180). Also, diagnosing GDM using a standardized OGTT with a fixed amount of glucose load should be a matter of upcoming research, as body composition and metabolically active tissue varies largely with height.

***Body size at birth.*** For women born small, the risk for developing GDM and other metabolic disturbances in adulthood is likely increased. Thus, collecting information on a woman's own birth anthropometry and early childhood growth should be a matter of interest. Also, a healthy and nutritious pregnancy diet is important for optimal fetal growth and should henceforth be supported in any pregnancy to prevent offspring being born either too large or too small, and thereby at risk for future metabolic disturbances and GDM.

***Smoking***. Smoking during pregnancy, measured with self-reported indicators, is mostly underestimated (267). Thus, intense intervention in women who report smoking should be highly encouraged, as the adverse effects of smoking seem to be reversible, at least to some extent, when it comes to glucose tolerance and fetal growth. However, findings of smoking on GDM in the literature are conflicting, and future studies should be made taking SES and gestational weight gain into account.

***Socioeconomic status.*** A low SES affects health adversely in general (299) and increases risk for GDM. Hence, women with low income and/or educational attainment in high-income countries should be identified. To support and offer personalized guidance for those pregnant women is important, and encouraging them to a healthier lifestyle, dietary habits and physical activity is essential in any disease prevention.

To summarize, to aim for a healthy pregnancy with positive implications for the whole family, identification of women at risk for GDM should be acknowledged not just during, but also before and in between, pregnancies. Public healthcare and risk identification should be a matter of interest for all clinicians, the woman herself, and public health policy-makers. It has been estimated that if GDM is prevented, it could save 240,000€ per person (estimated age at diagnosis 30 years, life cycle 84 years)(32). Public awareness of well-accepted traditional risk factors and new non-traditional ones is crucial to fight the growing burden of GDM on a population, individual and transgenerational level.

# 7 CONCLUSIONS

I Maternal height is inversely associated with GDM and short women are at greatest risk for developing GDM. The associations between GDM and offspring birthweight, as well as between maternal height and offspring birthweight, are positive. However, the interaction between GDM and maternal height on offspring birthweight is significant. If the pregnancy is complicated by GDM, offspring birthweight is increased only in women at extreme height levels, compared with women without GDM. In women of avarage height, offspring birthweight is not affected by GDM.

II Maternal body size at birth, estimated as BSA, is inversely associated with risk for GDM in Finnish primiparous women. Women born small are at greatest risk for developing GDM later in life.

III Smoking during pregnancy is positively associated with GDM. In women who continue smoking after the first trimester, offspring birthweight is decreased. However, if the pregnancy is complicated by GDM, offspring birthweight is not decreased, not even in the same group of women who continue smoking after the first trimester.

IV SES, assessed as maternal annual mean taxable income and educational attainment, is inversely associated with GDM.

# ACKNOWLEDGMENTS

This study has been carried out between 2017 and 2021 at the Department of Obstetrics and Gynecology and the Department of General Practice and Primary Health Care at the University of Helsinki and Helsinki University Hospital, in collaboration with Vantaa Health Center. My sincere gratitude goes to the people of these institutions, to *Professor Seppo Heinonen*, *Professor Juha Tapanainen* and *Professor Oskari Heikinheimo*, the administrative, former and current academic heads of the Department of Gynecology and Obstetrics and to *Professor Kaisu Pitkälä*, the administrative head of the Department of General Practice and Primary Health Care, for the friendly atmosphere, the positive attitude toward research and the opportunity to conduct my study. The financial support for the studies included in this thesis, as well as for my PhD studies from Folkhälsan, Svenska Kulturfonden, and the Hospital District of Helsinki and Uusimaa are additionally acknowledged.

There are many persons without whom this project would not have been possible and I owe my deepest thankfulness to all of them.

First of all, my three supervisors. *Adjunct Professor Merja Laine*, the head of the Vantaa birth cohort study, who professionally and determinedly guided me through these past years as a PhD student to my dissertation. I am forever grateful for all your help and your time spent on this project. *Professor Johan Eriksson*, who introduced me to this research project and provided me reasearch facilties for my studies. I admire your work in the field of science and appreciate all your constructive and insightful feedback regarding my research. *Miira Pettersson, PhD*, who represented the obstetrical expertise for this study. The preciseness and details you possess in this research field are impressive. I highly valued our phone conversations over the Atlantic during your time as a postdoctoral researcher in Canada.

My pre-examinators and official opponent. *Professor Leea Keski-Nisula* and *Adjunct Professor Antti Perheentupa,* who performed an immense work reviewing my thesis. Thank you for the valuable comments and insightful observations that improved this dissertation. *Adjunct Professor Helena Fadl*, thank you for the honor of accepting the invitation as my official opponent.

My co-authors, colleagues and collaborators. *Statistician Hannu Kautiainen, BSc,* who helped me with the statistical analyses. Thank you for the invaluable work and extensive experience you always offered me over a cup of coffee in the world of statistics. *Kristiina Rönö, MD, PhD*, who joined our group in the

end of my PhD project, one step-ahead. Although, over a short period, I am truly happy for the opportunity we had to reflect on research and life in general. *Professor Mika Gissler*, who lend a helping hand when it came to data collected from the Medical Birth Register. Thank you for the patience and vast expertise you offered me. *Marko Raina, MD* and *Pirjo Pennanen, MD, Doc Med,* who were much involved in the initiation of this study. Thank you for your important contribution in Vantaa City. *Professor Per-Henrik Groop* and *Adjunct Professor Maija Jakobsson*, who were part of my thesis committee group. I appreciate your commitment to this work. *Professor Kari Teramo*, with whom I have been privileged to reflect on the history of GDM. Thank you for the rewarding conversations. *Adjunct Professor Niko Wasenius,* with whom I shared the working space in the beginning of my research career. Thank you for the practical advice. *Alyce Whipp, BS, MPH*, who edited the language of my thesis. It was a pleasure to work with you.

Although, I have been working mostly on this dissertation during my maternity leaves and at home with small kids, the inspiration came from my clinical work at the Department of Gynecology and Obstetrics in *Jorvi Hospital 2014–2015*. I had the privilege to learn from and work alongside so many experienced and skilled physicians dedicated to their work and I want to thank all *these dear colleagues*.

I also want to express my gratefulness to the closest people, who have kindly supported me over the years. *My best friends from childhood, elementary, middle and high school* are thanked for long-term and sincere friendships; and my collueages from medical school, especially *group R15*, for all the joy and laughter together. *My parents-in-law Leena and Jussi* are thanked for their genuine encouragement and for helping out with our children when needed. *My siblings* are thanked for all the shared moments together, during both good and difficult times; and *my in-laws and extended family* for the company along the way, with a special thanks to *Helena*, who designed the cover of this book. *My mother Caroline* is thanked for her endless support and wisdom, and for encouriging me to find my own way. And *my late father Tomas*, who is deeply missed and never forgotten, for always believing in me.

Finally, *my husband Walter* — thank you for being there, for your love and companionship, and your positive attitude toward my PhD journey. And *our dear children Alexandra* and *Edvard*, the greatest gifts of my life — thank you for the happiness and meaning you give to my every day. You inspire me.

Espoo, January 2021

Senja Masalin

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